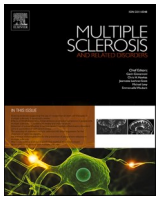
Multiple Sclerosis and Related Disorders 68 (2022) 104148

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Hypogammaglobulinemia: A contributing factor to multiple sclerosis fatigue?

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ARTICLE INFO

Keywords:
Multiple sclerosis
Fatigue
Immunoglobulin

ABSTRACT

Objective: Fatigue is one of the most disabling and difficult to treat symptoms of autoimmune diseases and frequently presents in people with multiple sclerosis (PwMS). Hypogammaglobulinemia for immunoglobulin G (IgG) affects approximately 8–25% of PwMS. We performed a retrospective analysis to investigate the association of MS-fatigue and IgG hypogammaglobulinemia.

Methods: PwMS, treated at Eginition University Hospital Athens or at the University Hospital Bern, were included (n = 134 patients (Bern n = 99; Athens n = 35)). Mann Whitney U-test (MWT), ANOVA test, Chi^2 test and multivariable linear regression models were run.

Results: 97/134 (72.4%) PwMS reported fatigue. In the multivariable linear regression analysis, IgG serum concentration (–1.6, 95%CI –2.7 - –0.5, p = 0.006), daytime sleepiness (0.8, 95%CI 0.2–1.4, p = 0.009), and a depressive mood (1.1, 95%CI 0.8–1.4, p < 0.001) were significantly associated with fatigue. The impact of IgG serum concentration (-2.9 95%CI -4.7 - -1.1, p = 0.002) remained significant also in the subcohort of PwMS without depressive symptoms or daytime sleepiness.

Conclusions: We found an association between IgG hypogammaglobulinemia and fatigue in PwMS (Level of Evidence IV), which might be translated to other autoimmune diseases. It bears a potential therapeutic consequence considering IgG supplementation strategies, if our finding can be validated prospectively.

1. Introduction

Fatigue is one of the most debilitating Multiple Sclerosis (MS) symptoms. It has a profound effect on quality of life and burden of disease, independently of physical disability (Runia et al., 2015; Krupp, 2006). Importantly, MS-related fatigue has far-reaching socioeconomic consequences leading to increased sick leaves and a higher probability of unemployment (Krupp, 2006). However, even though effective immunotherapies to treat autoimmune neuroinflammation and control MS-disease activity are available, effective treatment strategies for MS-fatigue are sparse and mainly include multimodal approaches, because of still unknown pathophysiological fatigue mechanisms. Fatigue is also present in other inflammatory diseases, cancer and immunodeficiency syndromes (Bower, 2014; Nocerino et al. 2020). Regarding the latter, 26–76% of the patients with primary immunodeficiency (PID) and common variable immunodeficiency (CVID) report fatigue (Janssen et al., 2018; Hajjar et al., 2017; Hajjar et al., 2018), which is more frequent than in the general population (Lerdal et al., 2005). In people with immunodeficiency, a connection between fatigue and upper respiratory infections has already been described (Hajjaret al., 2018). A pediatric study also showed a frequent occurrence of fatigue in patients with PID. In this study, the perceived fatigue was independent of presence and rate of infections (Nijhof et al., 2021). A recent Swedish study revealed that lower health-related quality of life and a higher prevalence of fatigue were reported among individuals with IgG hypogammaglobulinemia (Wågström et al., 2021). IgG

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https://doi.org/10.1016/j.msard.2022.104148
Received 18 June 2022; Received in revised form 4 August 2022; Accepted 25 August 2022
Available online 30 August 2022

hypogammaglobuliemia is a more common type of primary antibody deficiency. Hypogammaglobulinemia are diseases characterized by the "incomplete" absence of gamma globulins. In principle, they can be divided into congenital ("primary hypogammaglobulinaemia") and acquired forms ("secondary hypogammaglobulinaemia"). Autoimmune diseases appear in about 20 % of CVID patients and could be the first manifestation of the immunodeficiency (Agarwal and Cunningham-Rundles, 2009). Our group has demonstrated in a previous papter (Zoehner et al., 2019) high prevalence rates of reduced serum IgG concentrations regardless of immunotherapy affecting between 8–26% of the people with MS (PwMS). Similarly, IgA and IgM deficiency were also more common in this population than expected in the general population, at 3% and 12.5%, respectively. In addition, we identified in our previous paper (Zoehner et al., 2019) one patient out of 327 patients who fulfilled the diagnostic criteria of CVID being 31- to 310-times higher than expected (Zoehner et al., 2019). Consequences of IgG hypogammaglobulinemia in MS are partly unknown; however, fatigue might be one of them. The aim of our retrospective cohort study is to investigate whether IgG hypogammaglobulinemia is associated with fatigue in PwMS.

2. Methods

2.1. Patient population

PwMS, independent of the type of MS-disease and the immunotherapy, with available Fatigue Scale for Motor and Cognitive Function (FSMC) data and Immunoglobulin G serum concentration treated at the Eginition University Hospital Athens or at the University Hospital Bern between 08/2017 and 03/2020 were identified ($n = 162$). Of these 162 patients, 28 patients were excluded from analysis due to missing values in investigated variables resulting in a final cohort of 134 PwMS (Bern $n = 99$, Athens $n = 35$) (Fig. 1).

2.2. Data

The following patient data was extracted from medical records: FSMC-, Beck Depression Inventory (BDI)-II- and Epworth Sleepiness Scale (ESS)-scores, age, sex, Expanded Disability Status Scale (EDSS), MS-diagnosis, substance abuse, use of antidepressants, muscle relaxant, vitamin supplementation, bladder medication, fampridine, thyroid hormones, sleep medications, concurrent psychiatric disorder, thyroid disease, and other comorbid autoimmune diseases (Table 1A and supplement material 1). The following laboratory values were taken from the system of the respective central laboratory of each university hospital: serum concentration of IgG and C-reactive protein (CRP).

2.3. Assessment of fatigue, affective symptoms and daytime sleepiness

Fatigue was measured using the FSMC in the respective national language (German validated (Penner et al., 2009), Greek translated). The FSMC is a validated assessment of MS-related cognitive and motor fatigue. The questionnaire has 20 questions, which are scored from 1 to 5 resulting in a final score with a range from 20 to 100. Cutoff for the presence of at least mild fatigue is 43 points on the total score or 22 points on the motor or cognitive subscores (Penner et al., 2009). Affective symptoms were assessed via Beck Depression Inventory (BDI)-II and daytime sleepiness via Epworth Sleepiness Scale (ESS) (Beck et al., 1996; Johns, 1991). The following predefined cut-offs were used to define a presence of at least a mild depressive syndrome (BDI-II $\geq$ 14 points), a clinically relevant daytime sleepiness (ESS $\geq$ 11 points) or at least a mild fatigue (total fatigue $\geq$ 43 points, motor or cognitive fatigue $\geq$ 22 points).

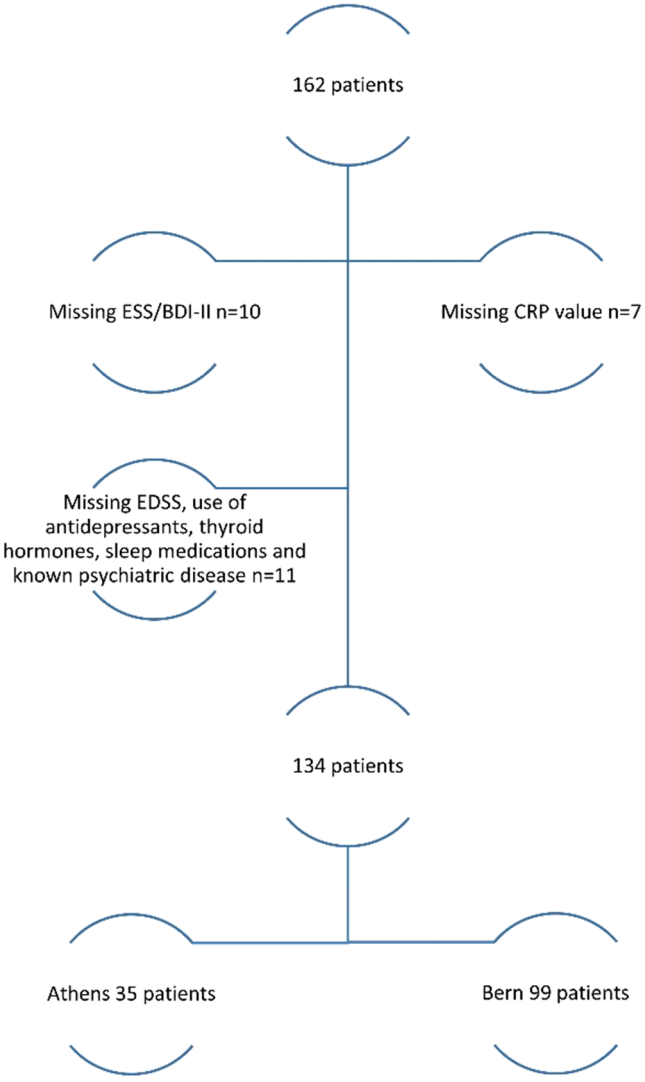

Fig. 1. Inclusion Tree
Abbreviations: BDI-II: Beck Depression Index-II; CRP: C-reactive protein; EDSS: Expanded Disability Status Scale; ESS: Epworth Sleepiness Scale.

2.4. Primary endpoint

Effect of IgG serum concentration on total FSMC score.

2.5. Secondary endpoint

Effect of IgG serum concentration on total FSMC score in PwMS without clinically relevant depressive symptoms (BDI-II score $<$ 14 points) and/or daytime sleepiness (ESS score $<$ 11 points).

2.6. Statistic

Continuous variables are presented as mean and 95% confidence intervals (95%CI) whereas categorical variables are reported as frequencies. Chi^2 test and multivariable linear regression analysis (MvReg) were run. The following independent variables were imputed in the MvReg with the dependent variable FSMC score: age, sex, center (Athens vs. Bern), immunotherapy and type of MS-disease. In this MvReg, the following variables were included separately: EDSS score, ESS score, BDI-II score, use of antidepressants, use of muscle relaxants, thyroid hormone replacement, use of sleep medication, substance/drug abuse, use of fampridine, use of medication to control bladder function,

Table 1
Classification of used medications (A) Multiple Sclerosis immunotherapy (B) and Comorbidities (C).

A Group of medications	Substance
Antidepressants	Melatonergic antidepressant; Multimodal antidepressant; Selective Serotonin Reuptake Inhibitor; Selective Serotonin-Noradrenalin-Reuptake-Inhibitor; Selective Noradrenalin-Dopamine-Reuptake-Inhibitor; Tetracyclic antidepressant
Muscle relaxant	Baclofen; Cannabinoids; Tizanidin; Tolperison
Bladder medication	Mirabegron; Solifenacin; Tamsulosin; Trospium
Sleep medications	Alprazolam; Bromazepam; Zolpidem
Thyroid hormones	Levothyroxin
Vitamin supplementation	Vitamin B-Complex and Vitamin D3 formulations
B	
Immunotherapies	n (%)
Any	116/134 (86.6)
No IT	18/134 (13.9)
1st line	37/134 (27.6)
Glatiramer acetate	8/134 (6.0)
Interferones	10/134 (7.5)
Teriflunomide	1/134 (0.7)
Dimethyl fumarate	18/134 (13.4)
2nd line	79/134 (59.0)
Fingolimod	23/134 (17.2)
Natalizumab	26/134 (19.4)
Ocrelizumab	14/134 (10.5)
Rituximab	10/134 (7.5)
Cyclophosphamide	6/134 (4.5)
C	
Comorbidities	
Psychiatric comorbidity	Includes in our study: Depressive disorder, bipolar disorder, psychotic disorder, attention deficit hyperactivity disorder, adjustment disorder, post-traumatic stress disorder
Autoimmune disease	Includes in our study: Polyarthritis, psoriatic arthritis, collagenous colitis, immune thrombocytopenia
Thyroid disease	Includes in our study: Hypothyroidism, Hashimoto's thyroiditis, Graves' disease, status post thyroidectomy.

Abbreviation: IT: Immunotherapy, n: number of cases.

presence of autoimmune comorbidity, presence of psychiatric comorbidity, presence of thyroid disease, serum concentration of CRP (mg/L) and IgG (g/L) (Table 1). Variables associated with the FSMC score with a level of significance greater than 95% (equal to $p < 0.05$) were included in addition to the baseline characteristics (age, sex, center, immunotherapy and type of MS-disease course) in the final combined MvReg. In this combined MvReg analysis, IgG serum concentration (g/L), BDI-II score and ESS score remained associated with FSMC total score. In this combined MvReg analysis, IgG serum concentration (g/L), BDI-II score and ESS score remained as significant predictors of FSMC total score. To test whether or not effect of IgG serum concentration on MS fatigue is also present in a cohort of MS patients without day time sleepiness (ESS score < 11 points) and without clinically relevant depressive symptoms (BDI-II score < 14 points), the combined MvReg was also run in this subgroup separately.

2.7. Ethics approval

This study was conducted within two ongoing registries approved by the local ethics committees of Eginition University Hospital Athens (1272018-511), and the Cantonal Ethics Committee Bern (KEK-BE: 2017-01369).

3. Results

3.1. Study population

Within the study population 87/134 (64.9%) were female, presented most commonly with a relapsing remitting MS course (123/134 (91.8%)) and a moderate degree of disability (mean EDSS (95%CI): 2.3 (2.0–2.6)). Mean age was 42.7 years (95%CI 40.5–45.0). 116/134 (86.6%) were treated with any immunotherapy and 2nd line treatments according to the European Medicines Agency (EMA) label were mainly used (79/116 (68.1%; Table 1B). Distribution of additional baseline characteristics are shown in Table 2.

3.2. Fatigue, depressive symptoms and daytime sleepiness

97/134 (72.4%) reported fatigue, whereas 89/134 (66.4%) reported cognitive and 103/134 (76.9%) motor fatigue as defined by FSMC. In the whole cohort, 44/134 (32.8%) patients reported at least mild depressive symptoms, all of whom were patients with at least mild fatigue (BDI-II ≥ 14 points + FSMC < 43 points vs ≥ 43 points: 0/37 (0%) vs 44/97 (45.4%); Chi^2 $p < 0.001$). An excessive daytime sleepiness (ESS ≥ 11 points), was found in 34/134 (25.4%) of the total population and was significantly more frequent in patients with at least mild fatigue, defined by FSMC values (ESS ≥ 11 points + FSMC < 43 points vs ≥ 43 points: 4/37 (10.8%) vs 30/97 (30.9%), Chi^2 $p = 0.025$).

3.3. Association with MS fatigue-multivariable linear regression (MvReg) analysis

MvReg models were adjusted for center, age, MS-diagnosis, sex and immunotherapy, demonstrating that fatigue assessed by FSMC was associated with EDSS, ESS, BDI-II, presence of psychiatric comorbidity, use of antidepressants and IgG serum concentration (Table 3A). These parameters were included in a combined MvReg model in which IgG serum concentration (–1.6, 95%CI –2.7 - –0.5, $p = 0.006$), ESS score (0.8, 95%CI 0.2–1.4, $p = 0.009$), and BDI-II score (1.1, 95%CI 0.8–1.4, $p < 0.001$) remained significant (Table 3B). To reduce the impact of these two confounders in the association between IgG serum concentration and fatigue, we ran the analysis in the subgroup of MS patients without clinical depressive symptoms (BDI-II score < 14 points) and without daytime sleepiness (ESS < 11 points) underlining the significant impact of IgG serum concentration on fatigue (–2.9, 95%CI –4.7 - –1.1, $p = 0.002$, Table 3C).

4. Conclusions

Our study demonstrated with a level IV of evidence a negative association of serum IgG concentration with fatigue in PwMS. MvReg analysis, which was controlled for relevant baseline characteristics and mimickers of MS fatigue, unmasked an association between IgG hypogammaglobulinemia and FSMC score with a coefficient being in the strength comparable with a depressive mood. This is remarkable as the latter is known to be a major contributing factor to fatigue and separation between these two is challenging. Our finding might be transferable to other autoimmune diseases, with an interconnection with IgG hypogammaglobulinemia.

This connection, where we cannot address causation by the data of our analysis, however bears therapeutic potential, as supplementation strategies with immunoglobulin replacement therapy are available. Hypothetically, also not shown by our data as CRP serum level was not associated with FSMC and infection rates were not available in medical records, one possible explanation of our finding is more frequent and possibly also subtle infections in patients with reduced IgG serum concentration. Findings in non-MS patients with immunodeficiency argue for infections as mediator. In detail, fatigue is common in patients with IgG hypogammaglobulinemia (Hajjar et al., 2017) and as demonstrated in a preliminary study is associated with rate of upper respiratory infections (Hajjar et al., 2018). In this study, patients with 0/1-2 upper respiratory infections within the last 12 months reported fatigue in 69.6/68.2% whereas those with ≥ 5 upper respiratory infections per 12 months reported fatigue in 88.0% (Hajjar et al., 2018).

Table 2
Patient characteristics.

Variable	Frequency (%)	Mean	95% Confidence Interval		Range		n
			Lower Limit	Upper Limit	Min	Max	
Female	87 (64.9)						134
Age (years)		42.7	40.5	45.0	19.3	80.1	134
Disease duration (years)		8.9	7.5	10.3	1.0	46	134
Scores							
EDSS		2.3	2.0	2.6	0	7	134
BDI-II		10.4	8.8	12.0	0	43	134
ESS		7.4	6.6	8.1	0	18	134
Medications							
Antidepressants	34 (25.4)						134
Muscle relaxants	14 (10.4)						134
Thyroid hormone replacement	9 (6.7)						134
Sleep Medication	11 (8.2)						134
Substance abuse	2 (1.5)						134
Fampridine	7 (5.2)						134
Bladder Medication	10 (7.5)						134
Comorbidities							
Other Autoimmune Disease	6 (4.5)						134
Psychiatric comorbidity	42 (31.3)						134
Thyroid Disease	10 (7.5)						134
Laboratory values							
CRP (mg/dl)		5.0	3.8	6.1	2.0	51	134
IgG		9.0	8.6	9.4	5.0	17.2	134
Immunotherapies							
No IT	18 (13.4)						134
Any	116 (86.6)						134
1st line	37 (31.9)						116
2nd line	79 (68.1)						116
MS disease course							
RRMS	123 (91.8)						134
SPMS	11 (8.2)						134
FSMC							
Total		57.1	53.6	61.0	20	95	134
Motor		29.7	27.9	31.6	10	50	134
Cognitive		27.3	25.6	29.1	10	46	134

Abbreviations: BDI-II: Beck Depression Index-II; EDSS: Expanded Disability Status Scale; ESS: Epworth Sleepiness Scale, FSMC: Fatigue Scala for Motor and Cognitive Function; IT: Immunotherapy; Max: Maximum; Min: Minimum; MS: Multiple Sclerosis; n: number of cases; RMS: Relapsing Multiple Sclerosis, SPMS: Secondary Progressive Multiple Sclerosis.

A recent study from Sweden investigated the severity of fatigue using the Fatigue Impact Scale (FIS) in individuals with immunoglobulin G subclass deficiency (IgGsd) but without MS. Participants with IgGsd had a significantly worse total fatigue score compared to controls. Accordingly, sixteen of the 35 subjects in the IgGsd group had FIS total scores between 60 and 138 representing moderate (score of > 38) to severe fatigue (score of > 80) (Fisk et al., 1994). In contrast, only one of the control subjects had a score of 66 points, indicating moderate fatigue (Fisk et al., 1994). Fatigue was also associated with the need for re-substitution of immunoglobulins in 18 of the participants. At baseline and at 36 months, those who continued immunoglobulin supplementation scored lower on the FIS than those who no longer received immunoglobulin supplementation (Wågström et al., 2021). A connection between immunoglobulin substitution and fatigue has already been shown in two studies investigation people with CVID. In CVID, fatigue has been attributed to a "wear off" effect in individuals subjected to intravenously administrated immunoglobulin substitution. (Hajjar et al., 2017; Chapel and Cunningham-Rundles, 2009)

The interconnection between infections and fatigue is further underpinned by the present SARS-CoV-2 pandemic where fatigue is one of the main symptoms during COVID-19 infection and afterwards as part of the Post-COVID-19 syndrome (Ortelli et al., 2021).

Therefore, we consider the retrospective nature of our study the main limitation leading to several missing values in clinical and laboratory assessments as well as missing radiological data to also incorporate MS lesion load and distribution into our investigation, which may also play a role in MS-fatigue. The setting of our study has to be addressed as this precludes especially investigations regarding the causation as discussed above. The presented study has led to a prospective observational trial (NCT05357781) to investigate, whether or not the association between IgG serum level and fatigue is mediated via infections (anticipated study completion date: November 30, 2023). Finally, we call other researchers to join data and forces to tackle this unmet need for patients with autoimmune diseases (contact via corresponding author).

Data sharing statement

Following an open data approach, anonymized data of the cohort can be requested via the corresponding author.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research

Key messages

(1) What is already known about this subject?

Fatigue is one of the most disabling multiple sclerosis (MS)-symptoms. However, treatment of MS-fatigue is still difficult. Hypogammaglobulinemia for immunoglobulin G (IgG) affects approximately 8-25% of persons with MS with partly unknown consequences.

(1) What does this study add?

In this retrospective study, we found an association between IgG

Table 3
Multivariable linear regression analysis. In all presented models (A–C) FSMC total score was the dependent variable and in addition to the independent variables displayed in the table all analysis (A–C) were adjusted for age, center (Bern vs Athens), diagnosis (RMS vs SPMS), gender, and treatment (no vs 1st vs 2nd line). (A) displays all independent variables in separate multivariable linear regression analyses (adjusted r2 and VIF (given only for significant predictors): EDSS: 0.12; each VIF < 2.0; ESS: 0.16; each VIF < 2.0; BDI-II: 0.49, each VIF < 2.0; Antidepressants: 0.14, each VIF < 2.0; Psychiatric Comorbidity: 0.17; each VIF < 2.0), IgG; 0.12; each VIF < 2.0). (B) displays a combined multivariable linear regression model including all variables presented in (A) and associated with the FSMC total score with a level of significance < 0.05 (adjusted r2 and VIF: 0.53, each < 2.0 except Antidepressants 2.1). (C) display the same multivariable linear regression model as presented in (B) focusing on the subcohort of 73 MS patients without comorbid depressive mood, defined as BDI-II score < 14 points, and without a comorbid daytime sleepiness, defined as ESS score < 11 points (adjusted r2 and VIF: 0.39, each < 2.0 except age 2.1, EDSS 2.3, Psychiatric comorbidity 2.1). Significant predictors are highlighted in bold letters. For definition of variables, we refer to Table 1. Abbreviations: BDI-II: Beck Depression Index-II; CRP: C-reactive protein, EDSS: Expanded Disability Status Scale; ESS: Epworth Sleepiness Scale; FSMC: Fatigue Scala for Motor and Cognitive Function; IT: Immunotherapies; MvREG: Multivariable linear regression analysis; n: number of cases; PwMS: People with MS, RMS: Relapsing Multiple Sclerosis; SPMS: Secondary Progressive Multiple Sclerosis, VIF: Variance Inflation Factor.

Variable	Coefficient	95% Confidence Interval		p-value	n
		Lower Limit	Upper Limit		
(A) MvReg analysis run separately for each listed variable					
EDSS	3.4	0.7	6.0	0.013	134
ESS	1.4	0.6	2.1	0.001	134
BDI-II	1.4	1.1	1.6	<0.001	134
Antidepressants	11.9	4.1	19.7	0.003	134
Muscle relaxants	1.7	-9.9	13.4	0.768	134
Thyroid hormone replacement	-6.5	-20.0	7.1	0.348	134
Sleep Medication	6.7	-6.4	19.8	0.312	134
Substance abuse	11.4	-16.1	39.0	0.413	134
Fampridine	9.1	-9.2	27.3	0.326	134
Bladder Medication	0.4	-13.0	13.9	0.951	134
Other Autoimmune Disease	-6.8	-23.3	9.7	0.418	134
Psychiatric comorbidity	15.0	7.3	22.7	<0.001	134
Thyroid Disease	-9.4	-22.4	3.6	0.153	134
CRP (mg/dl)	0.3	-0.3	0.8	0.333	134
IgG (g/L)	-1.9	-3.4	-0.4	0.014	134
(B) Combined MvReg analysis					
EDSS	1.4	-0.6	3.4	0.173	134
ESS	0.8	0.2	1.4	0.009	134
BDI-II	1.1	0.8	1.4	<0.001	134
Antidepressants	5.8	-0.9	12.6	0.089	134
Psychiatric comorbidity	-0.1	-7.4	7.2	0.975	134
IgG (g/L)	-1.6	-2.7	-0.5	0.006	134
(C) Combined MvReg analysis including PwMS without a depressive mood or daytime sleepiness					
EDSS	2.1	-0.8	5.0	0.154	74
ESS	0.2	-1.1	1.6	0.762	74
BDI-II	2.1	1.1	3.1	<0.001	74
Antidepressants	3.5	-8.0	15.0	0.542	74
Psychiatric comorbidity	4.2	-7.9	16.4	0.488	74
IgG (g/L)	-2.9	-4.7	-1.1	0.002	74

hypogammaglobulinemia and fatigue in MS-patients.

(1) How might this impact on clinical practice?

IgG hypogammaglobulinemia may be a potentially treatable immunological cause of MS-fatigue.

CRediT authorship contribution statement

L. Diem: Methodology, Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **M.E. Evangelopoulos:** Methodology, Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **D. Karathanassis:** Funding acquisition, Writing – review & editing. **V. Natsis:** Funding acquisition, Writing – review & editing. **N. Kamber:** Funding acquisition, Writing – review & editing. **H. Hammer:** Data curation, Writing – review & editing. **C. Friedli:** Funding acquisition, Writing – review & editing. **A. Chan:** Data curation, Writing – review & editing. **A. Helbling:** Data curation, Writing – review & editing. **I.K. Penner:** Data curation, Writing – review & editing. **A. Salmen:** Data curation, Writing – review & editing. **S. Walther:** Data curation, Writing – review & editing. **K. Stegmayer:** Data curation, Writing – review & editing. **R. Hoepner:** Methodology, Funding acquisition, Formal analysis, Data curation, Writing – review & editing.

Declaration of Competing Interest

Diem L received travel grants from Merck, Biogen, Roche and Bayer Schweiz. She also received advisory honoraria or speaker's honoraria from Biogen, Novartis and Merck. All not related to that work.

Evangelopoulos ME received travel grants and consulting fees from Biogen, Novartis, Genzyme, Teva, Merck, and Roche. All not related to that work.

Karathanassis D has no conflicts of interest.

Natsis V has no conflicts of interest.

Hammer H received research support and travel grants within the last 5 years from Biogen, Merck, Roche & BMS

Friedli C has received travel grants from Biogen, travel grants and advisory honoraria from Sanofi Genzyme, as well as speaker honoraria from Biogen, Novartis and Merck and research support from Chiesi, not related to this work. He reports no conflicts of interest related to this manuscript.

Kamber N received travel and/or speaker honoraria and served on advisory boards for Alexion, Biogen, Merck, Sanofi Genzyme and Roche and received research support by Biogen.

Salmen A received speaker honoraria and/or travel compensation for activities with Almirall Hermal GmbH, Biogen, Merck, Novartis, Roche, and Sanofi Genzyme and research support by the Swiss MS Society.

Chan A has served on advisory boards for, and received funding for travel or speaker honoraria from, Actelion-Janssen, Almirall, Bayer, Biogen, Celgene, Sanofi-Genzyme, Merck, Novartis, Roche, and Teva, all for hospital research funds; and research support from Biogen, Genzyme and UCB. Chan A is associate editor of the European Journal of Neurology and serves on the editorial board for Clinical and Translational Neuroscience and as topic editor for the Journal of International Medical Research.

Helbling A has no conflicts of interest.

Penner IK has received honoraria for speaking at scientific meetings, serving at scientific advisory boards and consulting activities from Adamas Pharma, Almirall, Bayer Pharma, Biogen, BMS, Celgene, Genzyme, Janssen, Merck, Novartis, Roche, and Teva. She has received research support from the German MS Society, Celgene, Novartis, Roche, and Teva.

Walther S received honoraria from Janssen, Lundbeck, Mepha, Neurolite, Otsuka and Sunovion. He served on advisory boards for Lundbeck and Sunovion in 2019. All interests are unrelated to this work. Dr. Walther is associate editor of the European Archives of Psychiatry and Clinical Neuroscience and Frontiers in Psychiatry, in addition, he serves on the editorial board of Neuropsychobiology.

Stegmayer K received honoraria from Janssen, Lundbeck, Mepha, and Sunovion. All interests are unrelated to this work.

Hoepner R received speaker/advisor honorary from Merck, Novartis, Roche, Biogen, Alexion, Sanofi, Bristol-Myers Squibb, and Almirall. He received research support within the last 5 years from Roche, Merck,

Sanofi, Biogen, and Bristol-Myers Squibb. He also received research grants from the Swiss MS Society. All not related to that work.

Acknowledgment

This article was supported by the MS Quality of life grant of the Swiss MS Society.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.104148.

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