

Fatigue and Associated Factors in Multiple Sclerosis Patients in Latvia

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Summary. *Background and objectives.* Fatigue is one of the most common symptoms of multiple sclerosis (MS). The aim of this study was to determine the presence of fatigue in MS patients in Latvia and its relation to lifestyle factors, neurological disability and depression.

Material and methods. This cross-sectional study included 117 participants (44 patients with MS and 73 healthy control group). Applied research instruments were: Expanded Disability Status Scale (EDSS), Patient Health Questionnaire (PHQ-9), Fatigue Severity Scale (FSS), and the general questionnaire for the collection of socio-demographic, lifestyle habits and clinical data constructed for the purposes of this study.

Results. Mean FSS score was 3.9 ± 1.9 in MS group. 26 (59.1%) patients had FSS score of 3.8 or more and were classified as a fatigue group (MSF) while 18 (40.9%) patients had FSS of 3.7 or less and were classified as a non-fatigue (MSNF) group. There was statistically significant difference between MSF and MSNF groups considering PHQ-9 score ($p=0.019$), FSS score ($p<0.001$) and EDSS score ($p<0.001$). Significant correlations of fatigue with depression ($r=0.48$, $p=0.001$), fatigue with neurological disability ($r=0.49$, $p=0.001$) and fatigue with smoking ($r=0.29$, $p=0.054$) were confirmed.

Conclusions. Fatigue is a common symptom in MS patients in Latvia. This study supports significant association between fatigue and clinical factors (disability, depression) and modifiable lifestyle factor – smoking.

Keywords: multiple sclerosis, fatigue, depression.

INTRODUCTION

Multiple sclerosis (MS) is a chronic, immune-mediated demyelinating disease of the central nervous system (CNS). It affects 2.3 million people worldwide, and is the most common cause of non-traumatic disability in young adults [1]. In 2015 there were 1801 patients registered in Latvia with MS diagnosis.

Fatigue is one of the most common symptoms of multiple sclerosis (MS). Thirty percent of patients present with fatigue, and it affects up to 90% of patients at some point

during their illness [1–3]. MS patients suffering from fatigue describe it as one of the worst and most debilitating symptom [4]. It is a common cause of early unemployment among these individuals, and has a negative impact on the quality of life [5, 6]. Due to the above-mentioned reasons, appropriate and effective management is very important.

In MS, fatigue can be divided into primary and secondary fatigue. Secondary fatigue is not an alternative diagnosis but may rather coexist and can contribute to the overall fatigue, but if recognized, secondary fatigue can be minimized [7, 8]. It is known that patients with MS are found to have a lifetime prevalence of depressive disorders of up to 50% [9], which is significantly higher than the 12.9% lifetime prevalence among patients with other chronic medical conditions [10]. Fatigue may arise independently of depression, or it can be an integral symptom.

Separation of treatable from untreatable causes of fatigue can be challenging in MS, however, the wide range of

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potential etiologies within this population makes MS a unique model for the study of fatigue [4]. The present study was designed in order to determine the presence of fatigue in multiple sclerosis patients and its relation to lifestyle factors, neurological disability and depression.

METHODS

This cross-sectional study included 117 participants (44 patients with MS and 73 healthy control group) who were assessed consecutively between 1st October 2015 and 31st January 2016. The study dealt with 44 patients with relapsing-remitting MS aged 20–69 years, who were treated at the Center of Multiple sclerosis, Pauls Stradins Clinical University Hospital in Riga. Inclusion criterion was a definitive diagnosis of MS based on the McDonald’s criteria [11]. Patients were excluded if they had the progressive type of the disease or had a relapse during the 30-day period before being included in this study. Control group was made of 73 healthy individuals matched for age and gender. The ones diagnosed with multiple sclerosis, chronic fatigue syndrome, and hepatitis B, as well as non-residents of Latvia were excluded.

Applied research instruments were: Expanded Disability Status Scale (EDSS) [12], Patient Health Questionnaire (PHQ-9) [13], Fatigue Severity Scale (FSS) [2], and the general questionnaire for the collection of socio-demographic, lifestyle habits and clinical data constructed for the purposes of this study. It included information on age, gender, education, level of disability, fatigue severity, depression scores and lifestyle factors (average hours of sleep, pet ownership, smoking, alcohol consumption, daytime sleeping, and physical activity).

All patients were examined at the time of recruitment. They underwent complete neurological examination. Physical disability was assessed using the Expanded Disability Status Scale (EDSS) [12]. Scores for the total scale can range from 0 (no neurological abnormality) to 10 (death from multiple sclerosis). Patients with a score of

3.5 were defined as fully ambulatory while patients with higher scores had ambulation limitations.

Level of depression was measured by the Patient Health Questionnaire (PHQ) which is a self-report measure for major depressive and subclinical depressive disorders and has been frequently used and extensively validated in multiple populations. The PHQ-9 queries each of the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) major depression criteria. The items address the past 2 weeks and are scored on a 4-point scale (0 = not at all, 1 = several days, 2 = more than half the days, and 3 = nearly every day). A score of 10 or higher indicates major depression (mild), 15 or higher moderate, and > 20 severe major depression [13, 14].

Fatigue was measured by the Fatigue Severity Scale (FSS) which shows high reliability, validity, and internal consistency [2] and has been the most widely used in MS studies [15]. It comprises nine items, each scored from

1–7 on a Likert scale, where 1 signifies no symptoms of fatigue and 7 indicates severe fatigue. Based on the mean results of control group, we considered a status of ‘fatigue’ when the FSS score was ≥ 3.8 , and a status of ‘non-fatigue’ with score < 3.7 .

The same questionnaires were distributed to the control group.

Ethics approval was granted by Ethics Committee of Riga Stradins University.

The *Shapiro-Wilk* test was used to test the continuous data for normal distribution. The independent *Mann-Whitney U* test was used to test for equal distribution between the control group and MS group. The cases were recorded into age groups (20–35, 36–50, 51–65, and >65) and compared in regards to difference in distribution of the FSS score, PHQ-9 score, and average hours of sleep during the night (between control and MS group).

The *Pearson’s* and The *Spearman* rank correlation coefficients, Mann Whitney U and Chi-square tests were used. All statistical tests were two-sided, and P-value less than 0.05 was considered as significant.

RESULTS

In total, we investigated 117 participants, 44 MS patients and 73 healthy controls. The mean age of the patients was 42.9 ± 12 years. 28 (63.6%) of the patients were female. The average EDSS score of the MS patients was 2.8 ± 1.7 .

Table 1.1 shows the comparison of demographic characteristics and education level between the MS patients and healthy controls.

We compared age, fatigue, depression levels and sleep duration between MS patients and control group (Table 1.2). Mean FSS score in MS group was 3.9 ± 1.9 , but in control group 3.84 ± 1.2 . PHQ-9 score in MS group was higher (7.7 ± 5.3) than in control group (5.1 ± 3). Average hours of sleep in both groups were similar – 7.22 and 7.23 hours.

Table 1.1. Comparison between patients with MS and controls: gender, education level

		Multiple sclerosis		Controls	
		Number	%	Number	%
Male		16	36.4	13	17.8
Female		28	63.6	60	82.2
Education	Less than high school	5	11.4	0	0
	High school	15	34.1	8	11
	College	1	2.3	2	2.7
	Professional degree	14	31.8	4	5.5
	Bachelor degree	7	15.9	21	28.8
	Master degree	2	4.5	35	47.9
	Doctoral degree	0	0	3	4.1
Total		44		73	

Table 1.2. Comparison between patients with MS and controls: age, fatigue, depression and sleep duration

	Multiple sclerosis	Controls
	Mean±SD	Mean±SD
Age	42.9±2.0	38±2
FSS	3.9±1.9	3.84±1.2
PHQ-9	7.7±5.3	5.1±3
Average hours of sleep	7.22	7.23

SD: standard deviation, FSS: Fatigue Severity Scale, PHQ-9: Patient Health Questionnaire

We compared lifestyle habits in both groups (Table 1.3). Regarding pet ownership, 63.6% of MS patients own a pet if compared to control group where only 31.5% have one. Sleeping habits in both groups are similar – 11.4% in MS group and 12.3% in control group sleep during the day. Physical activity level in MS patient group is lower (34.1%) than in control group (56.2%). 31.8% of MS patients are smokers, whereas only 17.8% of control group smoke. However, in control group 47.9% of people consume alcohol at least twice a week while in MS patient group 90.9% consume alcohol less than once a week.

26 (59.1%) patients had FSS score of 3.8 or more and were classified as a fatigue group (MSF) while 18 (40.9%) patients had FSS of 3.7 or less and were classified as a non-fatigue (MSNF) group. The mean FSS score for MS group was 3.9±1.9. In control group 53.4% (n=39) were fatigued while 46.6% (n=34) were not.

There was statistically significant difference between fatigue (MSF) and non-fatigue (MSNF) groups considering PHQ-9 score (p=0.019), FSS score (p<0.001) and EDSS score (p<0.001) (Table 2).

We explored the association between fatigue in MS and demographic factors, education level, disability, depression and lifestyle factors. Significant correlations of fatigue with depression (r=0.48, p=0.001) and fatigue with neurological disability measured by EDSS scale (r=0.49, p=0.001) was confirmed (Fig. 1, 2). There was weak positive correlation between fatigue and smoking (r=0.29, p=0.054) found in patients with MS. Moderate, positive,

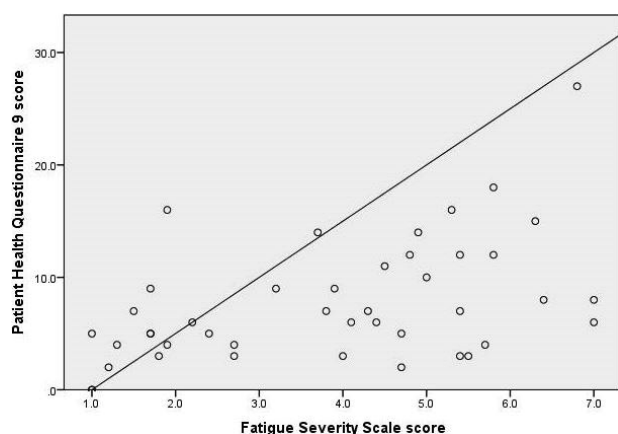


Fig. 1. Correlation between fatigue (FSS score) and depressive symptoms (PHQ-9 score) in multiple sclerosis patients

Table 1.3. Comparison between MS and healthy controls: pets, smoking, daytime sleeping, physical activity, alcohol consumption habits

		Multiple sclerosis		Controls	
		Number	%	Number	%
Pets	Pet owner	28	63.6	23	31.5
	No pets	16	36.4	50	68.5
Smoking	Smoker	14	31.8	13	17.8
	Non-smoker	30	68.2	60	82.2
Daytime sleeping	Yes	5	11.4	9	12.3
	No	39	88.6	64	87.7
Physical activity	None	29	65.9	32	43.8
	1-2 times per week	6	13.6	24	32.9
	3-4 times per week	2	4.5	12	16.4
	5-6 times per week	2	4.5	4	5.5
	7 times per week	5	11.4	1	1.4
Times consuming alcohol per week	<once	40	90.9	38	52.1
	1-2 times	4	9.1	18	24.7
	2-3 times	0	0	10	13.7
	3-4 times	0	0	3	4.1
	5-6 times	0	0	3	4.1
	7 times	0	0	1	1.4
Amount of alcoholic drinks* consumed in one sitting	1-2	27	61.4	50	68.5
	3-4	12	27.3	16	21.9
	5-6	3	6.8	3	4.1
	7-8	0	0	0	0
	9-10	1	2.3	2	2.7
	11-12	0	0	0	0
	13-14	0	0	1	1.4
	>15	1	2.3	1	1.4
Total		44		73	

*defined as 500 ml 5% beer OR 150 ml / one glass of 11% wine OR 50 ml 40% spirits

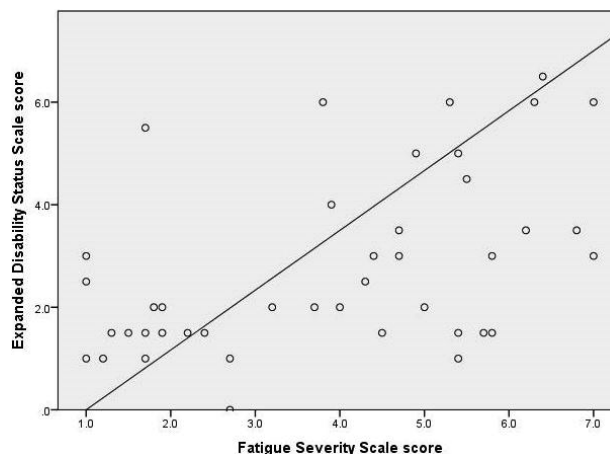


Fig. 2. Correlation between fatigue (FSS score) and neurological disability (EDSS score) in multiple sclerosis patients

Table 2. Relationship between fatigue and clinical characteristics in MS patients

	MSF (n=26)	MSNF (n=18)	P value
PHQ-9 score	25.76	16.78	0.019
FSS score	31.5	9.5	<0.001
EDSS score	27.15	13.97	<0.001

MS: Multiple Sclerosis, MSF: Multiple Sclerosis fatigue group, MSNF: Multiple Sclerosis Non Fatigue group, PHQ-9: Patient Health Questionnaire 9, FSS: Fatigue Severity Scale, EDSS: Expanded Disability Status Scale

statistically significant correlation of disability with depression ($r=0.38$, $p=0.012$) was also confirmed in MS group. In control group there was a significant correlation between fatigue and depression.

We did not find any association between fatigue and demographic factors, education level, sleeping habits, physical activity, alcohol consumption and pet ownership.

In this study, 27.9% (n=12) of the MS patients were depressed, only 8.2% (n=6) of the controls were depressed. There was a significantly higher FSS score ($p=0.008$) in depressed MS patients (Fig. 3).

DISCUSSION

Our study provides a unique, preliminary analysis of associations between demographic, clinical and lifestyle factors and clinically significant fatigue in Latvian population with MS.

In this study, 59.1% of the MS patients were fatigued. This number is close to that found in the international fatigue prevalence part of the HOLISM (Health Outcomes and Lifestyle Intervention in a Sample of People with Multiple Sclerosis) study with 2138 participants, where 65.6% of the participants were fatigued [16].

Identification of modifiable factors that may contribute to fatigue has been the subject of recent studies. We analyzed the association between fatigue and lifestyle factors that might minimize or exacerbate fatigue and found a tendency in our study which showed that smoking patients were more fatigued than non-smokers ($p=0.054$). 71.4% of smoking patients were fatigued while only 53.3% of non-smokers were fatigued. In a study by Fritz et al. [17], it was demonstrated that smokers, over time, had an increased rate of brain atrophy compared to non-smoking controls. The brain atrophy in MS is accelerated comparing to healthy controls [18], and smoking has been shown to worsen MS [19]. Considering facts mentioned above, MS patients could benefit from smoking cessation.

No significant associations were found between alcohol consumption habits and fatigue in our study. In the HOLISM study [16], moderate consumption of alcohol was associated with lower odds of fatigue. All of the MS patients in our study consumed alcohol less than twice a week, 90.9% less than once per week, and most of them less than four alcoholic beverages per week (88.7%). Be-

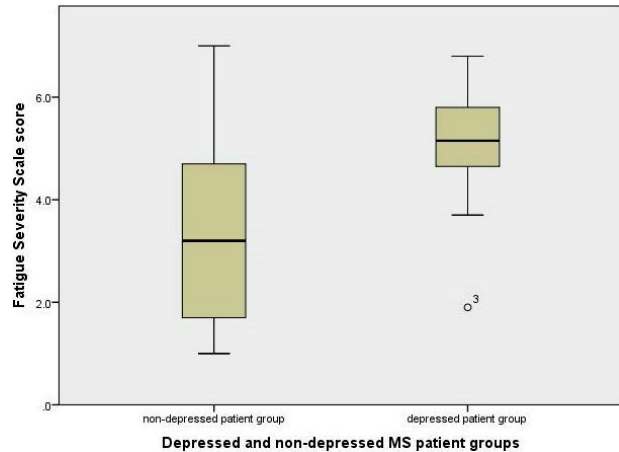


Fig. 3. Association between depressed and non-depressed groups and level of fatigue in MS patients

cause of the low consumption of alcohol among most of the MS patients, it is difficult to compare the results obtained. Recent studies show that alcohol (beer, wine or liquor) consumption is not associated to MS risk [20, 21]. However, alcohol should be considered as a molecule that interferes with the normal metabolism and facilitates the inflammatory process, complicating the possibility of improving the wellbeing of the patient [22].

Current studies suggest that persons with MS may have significantly more sleep problems than the general population, though prevalence estimates range from 25 to 54% [23–25]. Sleep disorders in MS and in the general population have a close association with symptoms of fatigue [26–28]. However, there was no association of sleep duration or daytime sleeping with fatigue in our study.

We did not find any association between fatigue and demographic factors, education level, physical activity, and pet ownership, unlike in the HOLISM study, where numerous demographic factors were associated with clinically significant fatigue. The factors distinguished among them included older age, female gender, and lower level of education [16]. Regarding physical activity, there is growing evidence that exercise affects fatigue in people with MS and vice versa [29]. It is therefore imperative to encourage exercise and physical activity from an early stage of the disease in the MS population.

Although it is hard to differentiate causes of fatigue in MS patients, correlation of fatigue with disability and depression in this study suggests the role of interplay between these clinical factors.

Higher fatigue rating was associated with a higher disability score in our study. Neurological disability measured by EDSS was also strongly related to fatigue in other studies [30–35]. But there are studies which demonstrate that perception of fatigue occurs in MS independently of the neurological impairment [36–38]. We should consider that assessing cerebral functional system score which is a part of EDSS, fatigue is already evaluated on a scale from 0 to 3. If a patient is severely fatigued (reduction of daily activities more than 50%) it affects total EDSS score respectively. However, total EDSS score in presence of pathological fatigue is only 2.0 if

other functional systems are not affected. Presence of fatigue in our MS patient group was in different levels of disability and probably was affected by secondary factors.

We found an association between disability and depression, and the level of physical activity. Neurological impairment explains the decline in physical activity, which in its turn could provoke development of mood disorders.

The prevalence of depression or depressive disorder in multiple sclerosis patients in meta-analysis which included 58 articles with a total sample size of 87,756 MS patients, was 30.5% [39]. In our study we obtained similar results – 27.9% of MS patients were depressed. An association between fatigue and depression was found, similar to the results obtained in other studies that showed correlation between depression and fatigue [33, 34, 36, 37, 40, 41]. Depressive symptoms increase the fatigue either directly or as a result of its psychological consequences [42–45]. Depressive mood may be interpreted as a reaction to being ill or as the result of (left) frontal neurodegeneration [46]. It has been argued that fatigue and depression in MS are both symptoms associated with similar neurobiological pathways [47]. Depression in MS patients is related to lower quality of life, cognitive dysfunction, elevated suicide risk, and working problems [48, 49]. Since depression in MS seems to worsen over time and as it is often treatable, early recognition is important and knowledge of its presence and management should be further improved in order to enhance clinical care [50–52]. Further studies are needed to determine whether depression treatment also improves fatigue in MS patients and whether antidepressant medications improve fatigue even in the absence of depression.

CONCLUSIONS

The results obtained in this study show that fatigue is a common symptom in MS patients of Latvia. Analyzing lifestyle habits in MS patient group, smoking patients were more fatigued than non-smoking patients, whereas other lifestyle factors did not show statistically significant associations with fatigue. In view of the above-mentioned findings, patients should be advised to give up smoking. Positive moderate correlations of fatigue with neurological disability and depression were confirmed, suggesting the role of these clinical factors leading to fatigue. Therefore, clinicians should increase awareness of modifiable factors and consider the interrelationship between these symptoms when treating either of them as it may be important for early therapeutic and prophylactic interventions.

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SERGANČIŲJŲ IŠSĖTINĖ SKLEROZE NUOVARGIS IR SUSIJĘ VEIKSNIAI LATVIJOJE

Santrauka

Įvadas ir tikslai. Nuovargis yra vienas dažniausių išsėtinės sklerozės (IS) simptomų. Šio tyrimo tikslas buvo nustatyti nuovargio

dažnumą tarp IS sergančių pacientų Latvijoje ir jo ryšį su gyvenimo veiksniais, neurologinė negalia ir depresija.

Tiriamieji ir tyrimo metodai. Į šį skerspjūvio tyrimą buvo įtraukta 117 tiriamųjų (44 IS sergantys ligoniai ir 73 sveiki kontroliniai asmenys). Taikyti tyrimo instrumentai buvo: Išplėstinė negalios įvertinimo skalė (*Expanded Disability Status Scale*, EDSS), Pacientų sveikatos klausimynas (PHQ-9), Nuovargio sunkumo skalė (*Fatigue Severity Scale*, FSS) ir socio-demografinių rodiklių, gyvenimo būdo įpročių ir klinikinių duomenų klausimynas.

Rezultatai. FSS rezultatas IS grupėje buvo $3,9 \pm 1,9$. 26 (59,1 %) pacientų FSS rezultatas buvo 3,8 ar daugiau. Šie pacientai buvo priskirti nuovargio grupei (MSF). 18 (40,9 %) pacientų FSS buvo 3,7 ar mažiau. Šie pacientai buvo priskirti IS be reikšmingo nuovargio (MSNF) grupei. Statistiškai reikšmingas įverčių skirtumas tarp MSF ir MSNF grupių nustatytas PHQ-9 ($p = 0,019$), FSS ($p < 0,001$) ir EDSS ($p < 0,001$). Nustatyta reikšminga nuovargio koreliacija su depresija ($r = 0,48$, $p = 0,001$), neurologinė negalia ($r = 0,49$, $p = 0,001$) ir rūkymu ($r = 0,29$, $p = 0,054$).

Išvados. Nuovargis yra dažnas simptomas tarp IS sergančių pacientų Latvijoje. Šis tyrimas patvirtina reikšmingą nuovargio ir klinikinių veiksnių (negalios, depresijos) ir modifikuojamo gyvenimo būdo veiksnio – rūkymo ryšį.

Raktažodžiai: išsėtinė sklerozė, nuovargis, depresija.

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