Psychiatria Danubina, 2015; Vol. 27, No. 4, pp 406-412 *Original paper*

FATIGUE DURING MULTIPLE SCLEROSIS RELAPSE AND ITS RELATIONSHIP TO DEPRESSION AND NEUROLOGICAL DISABILITY

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received: 11.6.2015; revised: 15.9.2015; accepted: 28.9.2015

SUMMARY

Background: *Fatigue is a common symptom of multiple sclerosis patients that may be present at all stages of the disease. The aim of this study was to determine presence of fatigue in multiple sclerosis patients during relapse and its relation to neurological disability and depression.*

Subjects and methods: *This cross-sectional study included 120 patients who were assessed during the acute relapse of relapsing-remitting multiple sclerosis. Applied research instruments were: general questionnaire, Expanded Disability Status Scale (EDSS), Beck Depression Inventory-II (BDI-II) and Fatigue Severity Scale (FSS). All patients were examined at the same appointment.*

Results: *54 (45%) patients were grouped into MS fatigue (MSF) group (FSS≥5) and 48 (40%) as non-fatigue (MSNF) group (FSS≤4). Mean FSS score was 4.83+/-1.49. Difference between MSF and MSNF patients was significant considering age ($p<0.001$), relapse severity ($p=0.044$), BDI score ($p<0.001$) and EDSS score ($p<0.001$). Positive correlations of fatigue (FSS) with age ($rho=0.41$, $p<0.001$), depression (BDI score) ($rho=0.61$, $p<0.001$) and neurological disability (EDSS score) ($rho=0.55$, $p<0.001$) were confirmed. After adjusting for depression, there was only weak positive correlation between fatigue and neurological disability ($rs=0.38$; $P<0.001$), while after adjusting for EDSS score, fatigue continued to correlate moderately with depression ($r=0.48$; $p<0.001$). Multiple linear regression analysis showed that BDI score ($beta=0.380$; $p<0.001$), EDSS score ($beta=0.336$, $p<0.001$) and the age ($beta=0.202$; $p<0.05$) are independently related to fatigue severity in this patients.*

Conclusion: *Fatigue is a frequent symptom during multiple sclerosis relapse. Depression and, to a lesser degree, disability but not relapse severity are independently related to the presence of fatigue. Depression and fatigue should be recognized and treated during standard relapse treatment. Further research might focus on other factors influencing fatigue during multiple sclerosis relapse including evaluation of fatigue at the different time points.*

Key words: *multiple sclerosis – fatigue - depression*

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INTRODUCTION

Fatigue is a common disabling symptom of multiple sclerosis (MS) patients. (Hadjimichel et al. 2008). It is defined as subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities (MSCCPG 1998). This symptom is "invisible" to others, which may lead to misunderstanding of the limitations imposed by such overwhelming feeling of tiredness (Flesner et al. 2008). Sixty-five to ninety-seven per cent of MS patients have significant fatigue and 15-40 per cent describes fatigue as the most disabling symptom of their MS (Bergamaschi et al. 1997, Bakshi et al. 2000, Wood et al. 2013). Fatigue in MS is presented by variety of forms, including acute fatigue localized to specific muscle groups and persistent, global fatigue that has an adverse effect on both physical and mental activity (Multiple Sclerosis Clinical Practice Guideline 1999). The exact etiology of fatigue in multiple sclerosis is not known. Peripheral and central mechanisms have been presented with no completely satisfactory explanation in both cases (Bakshi et al. 2000). It is known that demyelination as the product of the inflammatory process that underlies MS impairs axonal conduction which may contribute to centrally mediated MS fatigue through several mechanisms (Bakshi et al. 2003). Gender, psychosomatic mechanisms, or sleep dysfunction do not explaine presence of fatigue in multiple sclerosis patients. Still, recognition of fatigue is important because both pharmacologic and non-pharmacologic treatments can be effective (Bakshi et al. 2000).

Prevalence of fatigue and depression among persons with MS are varying, which is probably partly due to differences in study design and measurement instrument (Wood et al. 2013.) Previous studies on fatigue in multiple sclerosis and its relationship to neurological disability and depression have shown conflicting results. Some studies have shown positive correlations between fatigue severity and neurological dysfunction such as that measured by the Expanded Disability Status Scale (EDSS) (Krupp et al. 1995, Bergamaschi et al. 1997, Wood et al. 2013) while others have not (Krupp et al. 1988, Sandyk & Awerbuch 1994, Fragoso et al. 2009). The relationship between fatigue and depression in MS is also complex. Fatigue may arise independently of depression, or it can be an integral symptom. It can also be secondary to insomnia, which in turn may be directly attributable to MS, an adverse effect of disease-modifying treatment, or a symptom of depression. Fatigue

could also reflect varying combinations of one or more of these factors (Feinstein et al. 2014). Recent study showed that concurrent prevalence of the anxiety, depression and fatigue occurs significantly in MS ($p<0.001$), while depression rarely occurs alone or without concurrent anxiety and/or fatigue (Wood et al. 2013). Fatigue caused limiting energy and endurance and may affecting mood, outlook, and ability to cope with accompanying symptoms; it may also be generated by concomitant or associated disorders which require independent assessment and treatment (Feinstein et al. 2014). Fatigue may be present at all stages of MS (Bakshi et al. 2003). It may be present during relapse which is defined as an episode of neurological disturbance specific for MS, when the clinicopathological studies have established that the causative lesions are inflammatory and demyelinating in nature (McDonald et al. 2001, Polman et al. 2005).

We designed this study to determine presence of fatigue in multiple sclerosis patients during relapse and its relation to neurological disability and depression.

SUBJECTS AND METHODS

Subjects

This cross-sectional study included 120 patients who were assessed consecutively between 1st January 2011 and 31st December 2013 during the acute relapse of relapsing-remitting multiple sclerosis according to Mc Donald criteria (Polman et al. 2005) and treated at the Department of Neurology, Clinical Center University of Sarajevo. The study included patients between the ages 18-60 years. Patients were excluded if having progressive type of the disease. All patients signed written informed consents for participating in the study and local ethic committee approval was taken.

Methods

Applied research instruments were: general questionnaire constructed for the purposes of this study, Expanded Disability Status Scale (EDSS) (Kurtzke 1983), Beck Depression Inventory-II (BDI-II) (Beck et al. 1996) and Fatigue Severity Scale (FSS) (Krupp et al. 1989).

The questionnaire for the collection of socio-demographic and clinical data, constructed for the purposes of this study, included information on age, gender, disease duration, level of disability, fatigue severity and depression scores. 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) (Kurtzke 1983). EDSS is the standard measure of disease progression and the degree of neurological impairment in clinical practice and clinical trials scoring. It is divided into eight functional systems: pyramidal, cerebellar, brainstem, cerebral, bowel and bladder, sensory, visual, and other; impairment in each system is graded and then summed across the eight systems. Scores for the total scale can range from 0 (no neurological abnormality) to 10 (death from multiple sclerosis). A patient with a score of ≤3,5 are fully ambulatory while patients with higher scores have ambulatory limitations.

The relapse severity was graded as: mild (EDSS increase by 0.5 point, or 1 point change in one to three Functional system (FS) scores), moderate (EDSS increase by 1 or 2 points, or 2 points change in one or two FS scores, or 1 point change in four or more FS scores), or severe (exceeding prior criteria) (Mowry et al. 2009).

Depression was assessed by using the Beck Depression Inventory-II (BDI-II) (Beck et al. 1996). BDI-II is an objective self report assessment tool comprising 21 items, and one of the most commonly used for patients with multiple sclerosis. Recommended cut off point is set at 13. BDI-II was used in this study because evidence-based guidelines published in 2014 by the American Academy of Neurology (AAN) cautiously endorsed the BDI-II as the psychometric scale of choice for assessing people with MS (Minden et al. 2014).

Fatigue was measured by the Fatigue Severity Scale (FSS) which shows high reliability, validity, and internal consistency (Krupp et al. 1989) and has been the most widely used in MS studies (Tellez et al. 2005). 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. The mean score of the nine items provides the final FSS score. The questionnaires were always completed at the same appointment. EDSS, FSS. BDI-II, demographics and clinical data such as age, gender and disease duration were assessed.

Based on earlier studies, we considered a status of 'fatigue' when the FSS score was ≥5, and a status of 'nonfatigue' when the score was ≤4; and scores between 4.1 and 4.9 were considered to have borderline fatigue and thus were not placed into the group analysis, however their scores were used for correlational analysis of fatigue severity (Bakshi et al. 2000, Tellez et al. 2005).

Statistical Analyses

Statistical analysis was performed using the IBM SPSS version 21.0 for Windows system (SPSSInc. Chicago, Illinois, USA). Data are presented as mean ±standard deviation or as median with interquartile range (IQR, 25th to75th percentiles) dependent on normality of variables distribution. The Kolmogorov–Smirnov statistic with a Lilliefors significance level was used for testing normality of distribution. In the case of categorical variables, counts and percentages were reported. Differences between two groups were tested by non-parametric Mann Whitney U test. A Kruskal-Wallis test was conducted to determine if there were differences in FSS scores between three or more groups.

Distributions of FSS scores were assessed by visual inspection of a boxplot. Subsequently, pairwise comparisons were performed using Mann Whitney U Test with a Bonferroni correction for multiple comparisons. Chi-square test was applied for comparison of the categorical variables. Correlation of FSS score with age, disease duration, EDSS and BDI scores was determined using Spearman Rank Correlation Test. This included partial correlation to determine the relationship between FSS and HDI scores adjusting for EDSS score and the relationship between FSS and EDSS scores adjusting for HDI score. A multiple linear regression analysis was run to predict FSS score from gender, age, relapse severity, disease duration, EDSS and BDI scores. The assumptions of linearity, independence of errors, homoscedasticity, unusual points and normality of residuals were met. All statistical tests were two-sided, and P-value less than 0.05 was considered as significant.

RESULTS

The mean age of the patients included in the study was 40±11 years; range was 20 to 60 years with a median of MS disease duration of 6 years (IQR= 4 to 11). 82 (68.3%) of the patients were female. 54 (45%) patients had FSS score of 5.0 or more and were classified as fatigue (MSF) group while 48 (40%) patients had FSS of 4.0 or less and were classified as non-fatigue (MSNF) group. Mean FSS score was 4.83+/-1.49.

There was statistically significant difference between fatigue (MSF) and non fatigue (MSNF) groups considering age (p<0.001), relapse severity (p=0.044), BDI-II score (p<0.001), EDSS score (p<0,001) (Table 1). After performing Spearman Rank Correlation Test, significant positive correlation of fatigue (FSS) score with age (rho=0.41, p<0.001), BDI scores (rho=0.61, p<0.001) and EDSS scores (rho=0.55, p<0.001) was confirmed. (Table 2). There was moderate positive correlation between neurological disability measured by EDSS scale and fatigue (Table 2). This included significantly higher EDSS scores in MSF patients (Me=5.5; IQR=3.5 to 6.1) compared with MSNF group (Me=2.8; IQR=2.5 to 3.5) (U=436.0, z=-5.819, P<0.001). Spearman Rank Correlation Test revealed a moderate positive correlation between FSS and EDSS scores (rs=0.55; P<0.001) and after adjusting for depression severity (BDI score), there was only weak positive correlation between FSS and EDSS scores (rs=0.38; p<0.001) (Figure 1). There is moderate positive correlation between depression measured by BDI-II scale and fatigue (Table 2). This included significantly

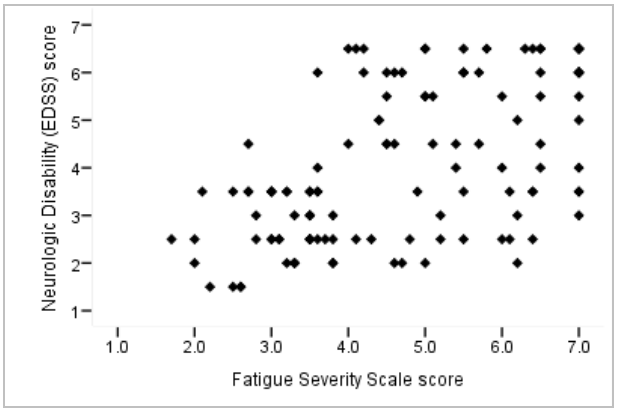

Figure 1. Correlation between fatigue (FSS score) and neurologic disability (EDSS score) in multiple sclerosis patients during relapse

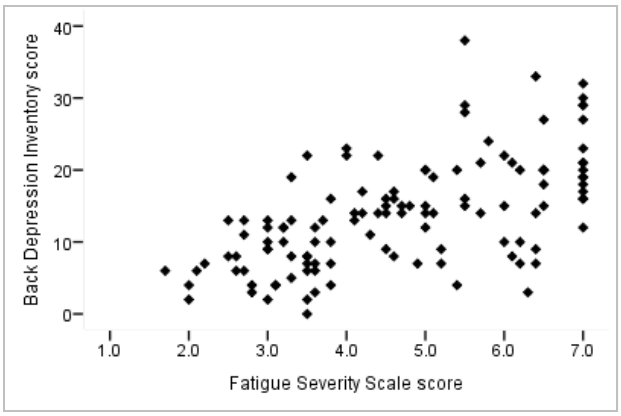

Figure 2. Correlation between fatigue (FSS score) and severity of depressive symptoms (BDI score) in multiple sclerosis patients during relapse

Table 1. Relationship between fatigue and demographic and clinical characteristics in multiple sclerosis patients during relapse

	MSNF *(n=48)*	MSF *(n=54)*	P value
Patient age (years)	31.0 (27.3 to 44.8)	45.5 (36.8 to 52.0)	*<0.001*
Male	31.3%	31.5%	*0.980*
Relapse severity			
Mild	16.7%	11.1%	
Moderate	75.0%	61.1%	*0 .044*
Severe	8.3%	27.8%	
Disease duration (years)	5.0 (3.1 to 10.0)	6.5 (4.0 to 12.3)	*0 .277*
BDI score	8.0 (5.3 to 12.0)	19.0 (14.0 to 21.3)	*< 0.001*
FSS score	3.2 (2.7 to 3.6)	6.3 (5.5 to 7.0)	*<0 .001*
EDSS score	2.8 (2.5 to 3.5)	5.5 (3.5 to 6.1)	*< 0.001*

MSNF- Multiple Sclerosis Non Fatigue Group; MSF-Multiple Sclerosis Fatigue Group; BDI- Beck Depression Inventory; EDSS-Expanded Disability Status Scale; FSS-Fatigue Severity Score

Table 2. Correlation of fatigue severity score with clinical findings in multiple sclerosis patients during relapse

Clinical findings	Correlation Coefficient	P value
Age (years)	0.41	*<0.001*
Disease duration (years)	0.18	*0 051*
BDI score	0.61	*<0.001*
EDSS score	0.55	*<0.001*

BDI- Beck Depression Inventory; EDSS-Expanded Disability Status Scale

Table 3. Multivariate regression analysis: predictors of fatigue severity in multiple sclerosis patients during relapse

Variables	B	SE_B	β
Intercept	1.230	0.563	
EDSS score	0.319	0.077	0.336**
BDI score	0.076	0.017	0.380**
Disease duration	-0.031	0.022	-0.109
Gender	-0.146	0.223	-0.045
Age	0.028	0.011	0.202*
Relapse severity	0.146	0.200	0.055

Note. ** p <0.001; * p <0.05, B= unstandardized regression coefficient; SEB = Standard error of the coefficient; β= standardized coefficient

higher BDI-II scores (Me=19.0; IQR=14.0 to 21.3) in MSF patients than MSNF patients (Me=8.0; IQR=5.3 to 12.0) (U=402.5, z=-5.997, P<0.001). Sperman Rank Correlation Test revealed a strong positive correlation between FSS and BDI-II scores (r=0.61; P<0.001) and after adjusting for EDSS score, there was still moderate correlation between FSS and BDI-II scores (r=0.48; P<0.001) (Figure 2). Gender, age, relaps severity, disease duration, EDSS and BDI scores statistically significantly predicted FSS score, F(6,113)=18.477, p<0.001, adj. R2=0.47. All six variables added statistically significantly to the prediction (p<0.05). Multiple linear regression analysis showed that depression (BDI-II score) (beta=0.380; p<0.001), neurological disability (EDSS score) (beta=0.336, p<0.001) and age (beta=0.202; p<0.05) are independently related to fatigue severity. Disease duration, gender and relapse severity did not contribute to the multiple regression model (Table 3).

DISCUSSION

The major finding of this study was that fatigue in multiple sclerosis was highly correlated and predicted independently by depression severity and neurological disability while relapse severity had no independent value in prediction of fatigue severity. The mean FSS score in this study was 4.83+/-1.49 with no difference comparing to other studies of fatigue in multiple sclerosis (mean FSS scores 4.7+/-1.6, 4.8+/-1.3 and 5.1+/-1.5 respectively) (Krupp et al. 1989, Valko et al. 2008, Amtmann et al. 2012). A difference between present and comparing studies is that other studies were not performed during relapse but they included patients with different type of the disease. This fact may influence the results since the higher levels of fatigue are confirmed in secondary progressive multiple sclerosis (SPMS) than in relapsing-remitting multiple sclerosis (RRMS). Patients with progressive type of disease were not included in this study.

In the present study, patients with fatigue (MSF) were significantly older comparing to patients with no fatigue (MSNF) with confirmed moderate correlation between fatigue and age that could be partially explained by higher neurological disability and higher depression scores in the group of older patients in this study. This result may also be associated with bigger influence of disease exacerbation on fatigue in older patients since in the other study fatigue and age were not correlated (Bakshi et al. 2000). In more recent study younger age was associated with increased fatigue (Wood et al. 2013). Fatigue showed no correlation with disease duration which is similar to the results of the other studies (Bakshi et al. 2000, Tellez et al. 2005, Wood et al. 2013).

In this study, there was no correlation between fatigue and gender which is same as in other studies (Bakshi et al. 2000, Tellez et al. 2005). Still, more recent study showed that more males than females had definite fatigue, and this was accounted for by higher levels of disability (Trojan et al, 2007, Wood et al. 2013). The strongest effect here was for the question on physical functioning, although after adjustment for the higher EDSS score in men, the sex differences in neither the overall score nor any individual question remained significant (Wood et al. 2013).

There was moderate positive correlation between neurological disability and fatigue which included significantly higher EDSS scores in MSF patients compared with MSNF group in this study. After adjusting for depression severity, there was only weak positive correlation between FSS and EDSS scores. Similar results were presented in other studies with moderate (rho=0.45) and weak correlation between FSS and EDSS scores which decreased to weak (rho=0.30) and no correlation respectively after adjusting for depression (Bakshi et al. 2000, Tellez et al. 2005). Neurological disability measured by EDSS was also strongly related to fatigue in more recent studies (Amtmann et al. 2012, Wood et al. 2013).

Correlation between depression and fatigue in this study remains moderate after adjusting for EDSS score. These results are similar to the results found in other studies that showed strong correlation between depression and fatigue, kept even after adjusting for disability (Bakshi et al. 2000, Tellez et al. 2005).

One of the challenges for correctly diagnosing depression in the context of multiple sclerosis is distinguishing whether a certain symptom emanates from a depressive disorder or can be attributed to the

demyelinating disease. These concerns regarding inclusion of items corresponding to neurovegetative symptoms which might lead to overdiagnosis as well as the length of the instrument, have led to the implementation of shorter forms, such as the 7-item Beck Depression Inventory-Fast Screen (BDI-FS) (Beck & Brown 2000). Validity of the instrument has also been documented for the population of patients with multiple sclerosis (Benedict et al. 2003). Even studies that used BDI-FS instrument, which excludes depression measures confounded with MS-related symptoms such as fatigue, found that fatigue was still significantly correlated with depression in MS patients (Morrow et al. 2009, Matiolli et al. 2011).

The association between fatigue and depression suggests that common underlying mechanisms play a role in depression and fatigue in multiple sclerosis such as psychological factors or speciphic brain lesions. Further study should determine if treatment of depression also improves fatigue in MS patients and whether antidepressant medications improve fatigue even in the absence of depression. Some studies have suggested no association between fatigue in multiple sclerosis and depression (Krupp et al. 1988, Vercoulen et al. 1996).

Considering relapse severity, there was significant difference between MSNF and MSF groups of patients with more patients with fatigue only in the group of patients with severe relapse.

Analyses considering gender, age, relapse severity, disease duration, EDSS and BDI scores statistically significantly predicted FSS score. Multiple regression analysis identified BDI-II, EDSS and age as independent predictors of the FSS score, while relapse severity was not. Depression severity showed the highest predictive value. Analyses in another study, considering depression, EDSS and disease duration as independent variables identified EDSS and BDI scores as independent predictors of the FSS score which is similar to the results of this study (Tellez et al. 2005).

Fatigue and depression showed high correlation during multiple sclerosis relapse same as during stable course of the disease with no important influence of relapse severity. This finding implicates importance of treatment of depression that might lead to improvement in fatigue independently of relapse treatment. Other authors also discussed effects of successful treatment of depression that might lead to a concomitant improvement in fatigue if it is a secondary problem. (Kroencke et al. 2000, Heesen et al. 2012). Fatigue may also exacerbate disability with the risk that underestimating the impact of fatigue is relative to the most serious complications of advanced disease (Bakshi 2003). Some less recent studies have suggested no association between fatigue in multiple sclerosis and depression. The lack of association between fatigue and depression in these studies could have been due to sample size, alteration of neurobehavioral findings by medications or the use of other measures of fatigue (Krupp et al. 1988, Vercoulen et al.1996). Previous data indicate that depressive symptoms can independently predict fatigue severity (Flachenecker et al. 2002). Improvement in depressive symptoms appears to be closely associated with decreased fatigue severity (Mohr et al. 2003). However, dysregulation of the hypo-thalamic–pituitary–adrenal (HPA) axis (evidenced by disruption of the diurnal pattern of cortisol secretion) has been shown in anxiety disorders (non-MS population) as well as in depression and fatigue in MS populations (Gottschalk et al. 2005, Wallin et al. 2006). The interaction between depression and fatigue also has significant implications for QOL (Wallin et al. 2006). Research on QOL indicates that the effects of depression on the overall well-being of patients with MS cannot be fully understood without consideration of the presence and severity of fatigue (Voss et al. 2002). Given that both depression and fatigue may independently affect QOL, depression affects the well-being of patients with MS cannot possibly be understood without an evaluation of fatigue (Wallin et al. 2006).

This is the first study conducted with the aim of analyzing different aspects of fatigue during multiple sclerosis relapse which is its major importance. Unfortunately, fatigue severity of multiple sclerosis patients before relapse was not considered which represents the major limitation of the current study. In addition, further research might focus on other possible factors influencing fatigue severity and treatment during multiple sclerosis relapse.

CONCLUSION

The results obtained in this study showed moderate correlation between fatigue and depression during multiple sclerosis relapse after adjusting for neurological disability. It was shown that depression and, to a lesser degree, disability but not relapse severity were related to the presence of fatigue. These findings may have important implications towards the care of multiple sclerosis patients. Both depression and fatigue are common and should be screened for carefully in all MS patients, regardless of neurological disability and disease course. Standard relapse treatment is also expected to improve fatigue and depression partially due to the disability improvement and partially as a result of underlying inflammatory condition treatment. Fatigue and depression were correlated but the relationship between them was moderate which implicates that the two entities are related but also different.

Acknowledgements: None.

Conflict of interest: None to declare.

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