The symptom of fatigue is a frequent complaint in multiple sclerosis (MS) patients. The aim of this study was to determine the link between fatigue and neurological disability, the duration of the disease and the subtype of the disease as well as to evaluate the specificity of three fatigue scales in this condition.

The study comprised 109 individuals with clinically definite MS: relapsing-remitting MS 79 (72.5%), secondary progressive MS 17 (15.6%), and primary progressive MS 13 (11.9%). Mean disease duration was 8.3 years. Mean EDSS (Expanded Disability Status Score) was 4.2 (range 1.0–8.0). Fatigue was measured by using the Fatigue Descriptive Scale (FDS), Fatigue Severity Scale (FSS) and Visual Analogue Scale (VAS). Fatigue was present in 92% of MS patients. The global FDS score was 5.1 ± 2.1 (range 1–10), FSS was 5.2 ± 1.5 (range 1.5–10) and VAS was 58.8 ± 22.4 (range 10–100). There was no significant correlation between the severity of fatigue and age and the duration of the disease by using any scale. FSS, FDS and VAS scores have not correlated with EDSS (p > 0.05). All three scales showed higher scores in patients with secondary progressive MS than in patients with relapsing-remitting MS and primary progressive MS, but the difference was not significant when FSS (p = 0.247) and FDS scales (p = 0.125) were used. FDS and FSS were highly correlated (r = 0.61, p < 0.0001).

Our results support the notion that fatigue is very frequently present in MS and suggest that it is not related to neurological impairment in these patients. Fatigue in MS is the most severe in secondary progressive MS.

Key words: multiple sclerosis; fatigue; disability

FATIGUE IN MULTIPLE SCLEROSIS: CORRELATION TO CLINICAL PARAMETERS

Svetlana D. Miletić Drakulić1, Jasna D. Jerđić2 and Jelena S. Drulović3
1Department of Neurology, Clinical Center Kragujevac; 2Department of Anesthesiology, Clinical Center Kragujevac; 3Institute of Neurology, Clinical Center of Serbia, Belgrade

SAŽETAK
Zamor je čest simptom u multipli sklerozi (MS). Cilj ove studije je da odredi odnos između zamora i kliničke onesposobljenosti, trajanja bolesti i forme multipli skleroze kao i da evaluira specifičnost tri skale za zamor.

Ispitano je 109 bolesnika sa klinički definitivnom MS: 79 (72.5%) bolesnika sa relapsno-remitentnom formom MS, 17 (15.6%) sa sekundarno progresivnom i 13 (11.9%) sa primarno progresivnom MS. Prosječno vreme trajanja MS bio je 8.3 godine. Srednji stepen funkcionalne onesposobljenosti (EDSS) skor bio je 4.2 (rang 1.0–8.0). Zamor je meren korišćenjem Deskriptivne skale zamora (FDS), Fatigue Severity Scale (FSS) i Vizuelno analognom skalom (VAS). Fatigue je bio u 92% bolesnika sa MS. Globalni FDS skor je bio 5.1 ± 2.1 (rang 1–10), FSS je bio 5.2 ± 1.5 (rang 1.5–10) i VAS je bio 58.8 ± 22.4 (rang 10–100). Tuđina zamora nije značajno korelirala s dužinom trajanja bolesti niti sa stepenom onesposobljenosti (EDSS skor) (p > 0.05). Bolesnici sa sekundarno progresivnom formom MS su imali viši skor zamora nego relapsno-remitentna i primarno-progresivna forma MS, ali razlika nije bila statistički značajna kada je korišćena FDS skala (p = 0.247) i FDS skala (p = 0.125). Nalazi na FDS i FSS skalama su visoko korelirali (r = 0.61, p < 0.0001).

Naši rezultati ukazuju da je zamor vrlo čest simptom MS i da ne korelira značajno sa kliničkom onesposobljenosti. Najteži zamor se javlja u sekundarno progresivnoj formi bolesti.

Ključne reči: multipla skleroza, zamor, onesposobljenost

INTRODUCTION
Fatigue is one of the most common and most disabling symptoms in multiple sclerosis (MS), which can also influence the quality of life of MS patients (1–4). According to many reports, the prevalence varies from 769–2% of cases (5–7). The symptom of fatigue is defined as the feeling of tiredness, lack of energy or lassitude (8). Fatigue is a complex symptom that includes three clinical different entities: asthenia (fatigue at rest, without exercise), fatigability and worsening of symptoms with effort (5,9). It is distinguished from the symptoms of depression, which include lack of self-esteem, despair, or feelings of hopelessness. Fatigue is also distinct from the limp weakness.

The exact etiology of fatigue in MS is unclear. In MS, pathogenic mechanisms proposed for fatigue have included immune dysfunction with release of pro-inflammatory cytokines: interferon (INF)-γ, tumor necrosis factor (TNF)-α and interleukin (IL)-1 (10). Although peripheral mechanisms have some role in the pathogenesis of fatigue, there are clear indications that central abnormalities play a more important role in MS. Neurophysiological studies are consistent with a presumed central origin of fatigue in MS and suggest a significant role for cortical dysfunction of frontal areas in these patients (11,12). Recent positron emission tomography (PET) study has shown that hypometabolism in the bilateral frontal cortex and basal ganglia is associated with fatigue in MS and it has hypothesized that cortical-subcortical disconnection may underlie fatigue (13,14). The study, which has used functional magnetic resonance imaging (fMRI), provides additional evidence that fatigue in MS is related to impaired interactions between functionally related cortical and subcortical areas (15).

The aims of this study were: (1) to determine the relationship between fatigue and demographic data, disease duration and neurological disability (EDSS) in MS patients (2) to evaluate the fatigue severity in three different forms of MS, and (3) to compare three widely used scales for measuring the severity of fatigue.

MATERIAL AND METHODS
Patients were selected consecutively from the Out-Patient Clinic of the Institute of Neurology, Clinical Centre
of Serbia, Belgrade and the Centre of Neurology in Kragujevac (in the period from January 1\textsuperscript{st}, 2001 till December 31\textsuperscript{st}, 2001). One hundred and nine patients (73.4\% of women, 26.6 \% of men) with clinically definite MS, diagnosed according to Poser’s criteria (16), age 40.9±10.4 years (range 106–4) with duration of the disease, 3±7 years (range 0.53–1) were studied (table 1).

**Table 1. Clinical findings in MS patients**

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Female-to-male ratio</th>
<th>Age Mean±SD</th>
<th>Disease duration Mean±SD</th>
<th>EDSS Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRMS</td>
<td>79</td>
<td>60.19</td>
<td>39.8±10.9</td>
<td>0.71±6.57</td>
</tr>
<tr>
<td>SPMS</td>
<td>17</td>
<td>15.2</td>
<td>44.6±7.1</td>
<td>12.41±9.35</td>
</tr>
<tr>
<td>PPMS</td>
<td>13</td>
<td>5.8</td>
<td>43.4±9.4</td>
<td>6.38±2.9</td>
</tr>
<tr>
<td>total</td>
<td>109</td>
<td>80.29</td>
<td>40.9±10.3</td>
<td>8.29±7</td>
</tr>
</tbody>
</table>

**Note:** RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; PPMS = primary progressive multiple sclerosis

MS patients diagnosed with anemia, liver or kidney disease were rejected from the study. Patients who were on psychoactive medications in the past two months that might have affected fatigue (eg., steroids, amantadine, or antidepressants) were also excluded.

Seventy-nine patients (72.5\%) suffered from relapsing-remitting MS, while seventeen patients (15.6\%) had secondary progressive and 13 (11.9\%) primary progressive disease.

The Fatigue Descriptive Scale (FDS), Fatigue Severity Scale (FSS) and Visual Analogue Scale (VAS) were used to evaluate fatigue. The Fatigue Descriptive Scale includes information regarding the modality of fatigue, spontaneity in the narration of the symptoms, severity, frequency, and the existence of Uhthoff phenomenon (heat dramatically worsens fatigue) (17). The range in the FDS is 0–17. The Severity Scale (FSS) is a nine-statement interview, from which an average score is determined on seven-point scale (18). In the Visual Analogue Scale subjects were asked to indicate the point on a 10-cm line ranging from „no fatigue“ to „severe fatigue“ that best described their fatigue (1).

Based on FSS scores, patients were divided into two groups: fatigue (MSF) with FSS score of 5.0 or more (n=63) and non-fatigue (MSNF) with FSS of 4.0 or less (n=27). Patients with FSS scores 4.1–4.9 (n=19) were estimated to have borderline fatigue and thus they were not placed into the group analysis of fatigue severity; however their scores were used for the correlational analysis of fatigue severity (19).

Statistical analysis was performed, by using Descriptive Statistics techniques, as well as procedures for non-parametric distribution techniques (Spearman Rank, Kruskal-Wallis ANOVA, Mann-Whitney, chi-square). The Spearman’s Rank correlation coefficients were calculated to explore any relationship between quantitative variables. The Kruskal – Wallis one-way analysis of variance (ANOVA) and the Mann-Whitney technique were used to study the differences in the score between groups. Chi-square was used to compare the frequency in qualitative variables.

**RESULTS**

In our study, 100 (91.7\%) out of 109 MS patients complained of fatigue. Only 9 (8.3\%) of these patients did not feel fatigue and they all had relapsing-remitting form of MS. Majority of MS patients with fatigue (64.4\%), described it as fatigue with exercise (fatigability), 21.8\% (n=22) as asthenia (fatigue at rest), 13.9\% (n=14) as worsening of other symptoms (paresthesias, blurred vision, and unsteadiness after exercise). Descriptions of fatigue were not significantly different between different forms of MS (p=0.341; p>0.05). For 16.8\% of MSF patients, fatigue was the most severe MS symptom, while 47.5\% of MSF patients (n=48) considered it as one out of three most disabling symptoms. The majority of patients with fatigue (80.2\%) report that heat dramatically worsens fatigue (Uhthoff phenomenon). This sensitivity to heat was a feature similarly shared by all forms of MS (p>0.05).

The global FDS score was 5.03± 2.58 (range 1–13), while FSS score was 5.15 ±1.53 (range 1.5–10.0). VAS score was 58.8± 22.4 (range 1–100). There was no difference between the sexes by using any scale. There was no significant correlation between the severity of fatigue and age as well as the fatigue and duration of the disease by using any scale. FSS score (r=0.27; p>0.05), FDS score (r=0.35; p>0.05) and VAS score (r=0.68; p>0.05) did not correlate with the level of neurological impairment, measured by EDSS score.

Fatigue was weakly associated with clinical course of MS. There was not any significant difference among three clinical courses of MS when FDS scale (p=0.129; p>0.05) and FSS scale were used (p=0.247; p>0.05). FSS score and FDS score were higher in patients with secondary progressive MS than in patients with relapsing-remitting MS and primary progressive MS. When VAS scale was used, there were significant differences among three clinical courses of MS (p=0.022; p<0.05), but also VAS scores were the highest in patients with secondary progressive MS (table 2).

**Table 2.** Visual Analogue Scale (VAS), Fatigue Severity Scale (FSS) and Fatigue Descriptive Scale (FDS) used to compare fatigue in different forms of multiple sclerosis

<table>
<thead>
<tr>
<th>Scale</th>
<th>RRMS Mean±SD</th>
<th>SPMS Mean±SD</th>
<th>PPMS Mean±SD</th>
<th>significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSS</td>
<td>5.03±1.7</td>
<td>5.7±1.04</td>
<td>5.07±1.1</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>FDS</td>
<td>4.9±2.6</td>
<td>5.9±2.5</td>
<td>4.5±2.3</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>VAS</td>
<td>96.5±20.8</td>
<td>70.6±18.8</td>
<td>56.1±30.7</td>
<td>P&lt;0.05</td>
</tr>
</tbody>
</table>

Note: RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; PPMS = primary progressive multiple sclerosis

FDS and FSS of Krupp were highly correlated. The Spearman R coefficient was high when compared with the global score (r=0.688; p=0.000). There was a significant correlation between FSS and VAS (r=0.595; p<0.000), as well as between FDS and VAS (0.588; p<0.000).
DISCUSSION
In our study, fatigue as a symptom appeared in a high percentage of patients (91.7%). Previous reports revealed that between 76 and 92% of MS patients experience fatigue (17, 20). It is remarkable that, in our study, most of the patients (62%) noticed the existence of fatigue only when asked about it, while a small number of patients spontaneously reported the occurrence of abnormal fatigue. The patients with spontaneously reported fatigue had higher scores on the FDS and FSS as well as on the VAS scales. It has been suggested that fatigue is a complex symptom that includes three clinical different entities (asthenia, fatigability and worsening of symptoms with effort). In our study, majority of patients (64.4%) defined the symptom as fatigue with exercise (fatigability), in accordance with the previous series (17). The patients with fatigability insisted that the fatigue was abnormal, stressing that in the past years, the same type of exercise had not produced any feeling of fatigue. It improved with rest in all patients. Twenty-two per cent of patients described the symptom as asthenia, fatigue at rest. The fact that patients with asthenia had higher FDS and FSS scores was compatible with the results of other authors (5, 17). Additionally, a patient who recognizes feeling of tiredness at rest, is tired in the exercise as well. Recent study has indicated that the severity of pyramidal involvement was associated with fatigability while some immunoactivation parameters were associated with asthenia (5).

In our study, MS fatigue was not significantly correlated with the level of neurological impairment measured by the EDSS score. Previous studies correlating MSF and EDSS led to conflicting results. Thus, Sandroni showed that there was no change in the pyramidal conduction in fatigued conditions (11). On the other hand, some authors found that the severity of pyramidal involvement was more exaggerated and that EDSS score was significantly higher in patients suffering from fatigue (5, 21, 22).

We can conclude that the FSS score and FDS score as well as VAS score were higher in patients with secondary progressive MS compared with patients with relapsing-remitting MS and primary progressive MS, but the difference did not reach the level of statistical significance when the FSS and FDS scales were used (table 2). These results are in accordance with prior studies (2, 21). When we used the VAS scale, the difference between different forms of MS reached the level of statistical significance. The explanation for these different results was in the fact that the VAS scale does not assess qualitative aspects of fatigue. A variety of instruments has been developed to assess fatigue in MS. The fatigue is a subjective experience and the most appropriate measure of the symptom is a self-report instrument which can quantify what patients experience. We proposed three scales as a tool to evaluate the severity and quality of fatigue in patients suffering from MS. The FSS and VAS scales as well as the FDS and VAS scales were significantly correlated, but the FSS and FDS scales were even more highly significant in correlation. The FSS assesses the effect of fatigue on activities of daily living (7) while FDS helps in classifying and defining periodicity and severity of fatigue in MS patients (17).

Fatigue in MS is probably related to the underlying pathologic alterations in MS such as demyelination, inflammation and axonal injury (19). The results of conventional MRI studies of the brain did not explain the nature of fatigue in MS and its pathogenesis is poorly understood (15). Possible explanation for inability of the brain MRI findings to explain fatigue in MS is that conventional MRI gives little information about the pathologic substrate of MS lesions and it doesn’t show microscopic damage in the normal-appearing white matter (NAWM) and the normal-appearing gray matter (NAGM) (23,24). However, inability to associate fatigue with MRI white-matter lesions suggests that direct involvement of cortical and subcortical gray matter rather than diachisis should be further explored as a cause of fatigue. Recent neuroimaging study with the use of functional magnetic resonance (fMRI) has provided evidence that fatigue in MS is related to impaired interactions between functionally related cortical and subcortical areas (15). Significant inverse correlations were found between the FSS scores and relative activations of contralateral intraparietal sulcus, ipsilateral Rolandic operculum and thalamus. Patients with fatigue showed more significant activations of the contralateral cingulated motor area. This area was included in different phases of movement planning and execution and it might have had a compensatory role in patients with fatigue who implied more efforts into performing some task. This study presents fatigue in MS as a frequent and disabling symptom. Our findings suggest that fatigue is not related to neurological impairment in these patients. We conclude that fatigue is more severe in secondary progressive MS versus relapsing-remitting and primary progressive form of MS. The specific fatigue scale is a good tool for exploration of this symptom of MS.

REFERENCES