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FATIGUE AND DEPRESSION IN MULTIPLE SCLEROSIS: CORRELATION WITH QUALITY OF LIFE

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Abstract - The aim of this work was to examine the relationship between fatigue and depression, common features of multiple sclerosis (MS), and the quality of life (QOL). The study was comprised of 120 patients with clinical manifestations of definite MS. Relapsing-remitting MS was present in 76.7% patients and secondary progressive MS was present in 23.3% patients. Mean disease duration was 8.1 ± 5.6 years and the mean Expanded Disability Status Score (EDSS) was 3.5 ± 1.8 (range 1-8). Fatigue was measured with the Fatigue Severity Scale (FSS), depression was measured by the Beck Depression Inventory (BDI) and QOL was assessed using the health-related quality of life questionnaire SF-36. We observed that the global FSS score was 4.6 ± 1.8 (range 1-7) and BDI was 10.7 ± 10.3 (range 0-39). The FSS significantly and positively correlated with the BDI scores (r = 0.572; p = 0.000). The severity of fatigue had a significant impact on the quality of life (r = -0.743; p = 0.000), in particular on mental health (r = -0.749; p = 0.000). We observed a significant correlation between the severity of depression and impaired quality of life (r = -0.684; p = 0.000). This study shows that fatigue and depression are associated with impaired QOL in MS.

Key words: Multiple sclerosis, fatigue, depression, quality of life

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INTRODUCTION

Fatigue and depression are often part of clinical manifestation in patients with multiple sclerosis. Fatigue is considered one of the most frequent symptoms of multiple sclerosis (MS). According to different studies, its prevalence is 53-95% in patients with MS (Krupp et al., 1988, Iriarteet et al., 2000). For some patients, fatigue is one of the most disabling symptoms that aggravates other symptoms. The severity of fatigue is often increased with the rise of outside temperature and physical effort. The influence of fatigue on the quality of life is apparent. The pathological physiology of fatigue has not been completely explained yet. This is due to the complexity of the symptom of fatigue itself. In the symptoms of fatigue, the physical and mental components are often differentiated, which is incorporated into the fatigue severity scale (Ford et al. 1998)

Depression is also a frequent symptom, ranging from 40%-60% in MS patients (Bakshi et al., 2000, Minden et al., 1990). The relation of fatigue and depression has been the subject of numerous studies. While some authors think that fatigue is a manifestation of depression, others have the opposite standpoint. Depression may considerably affect the course of disease, therapy and rehabilitation, thus noticeably impairing the quality of life (QOL).

The aim of this study was to determine the frequency and severity of fatigue and depression as well as their relations in MS patients and to evaluate the impact of fatigue and depression on the quality of life, independent of neurologic disability.

METHODS AND PATIENTS

The study included 120 patients who were regularly examined at the Clinic of Neurology, Clinical Centre Kragujevac, from 1 January 2006 to 30 December 2008.

The patients included fulfilled the following criteria: MS diagnosed according to Mc Donald (Polamn et al., 2005), age 18-60, disability status EDSS score 8 and less than 8.

The patients with exacerbation of the illness within the last month, or with other neurological, systemic (hematological, vascular, gynecological, endocrine, urological) or previously verified psychiatric and cognitive illnesses, as well as those who used medicaments with possible impact on mood, fatigue and cognition (anti-depressives, anxiolytics, interferon beta) within last two months, were not included in the study.

Demographic data of the patients and clinical data such as length and form of disease were evaluated by a neurologist. A neurologist also examined the patients and determined the disability status using EDSS (Expanded Disability Status Scale) (Kurtzke et al. 1983).

FSS (Fatigue Severity Scale) was used in the evaluation of fatigue severity (Krupp et al., 1989). Among those most often used, the Fatigue Severity Scale is focused on the physical symptoms of fatigue. It includes 9 questions, whereby the patient ranges his answers from 1 to 7, depending on his complete agreement (7) or disagreement (1) with the statement.

Based on the FSS score, the patients were classified into two groups: those with fatigue (MSF), FSS score 5 and above, and those without fatigue (MSNF), score of 4 or less. The patients scored between 4.1-4.9 were felt 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).

Depression was diagnosed using the DSM-IV criteria for depression symptoms (1994), and its severity was evaluated using the Beck Depression Inventory (BDI) (Beck et al., 1961). This scale includes 21 questions to be answered by the patient regarding his/her mood in the last four weeks. The cognitive, somatic, and motivational aspects of depression are graded.

The special questionnaire SF-36 (Medical Outcomes Study Short Form 36-item Questionnaire) with eight domains of life (Jekinson et al.,1993) was used as an instrument in the evaluation of life quality. The scale considers physical health (14 questions), emotional (3 questions) and social functioning (2 questions), mood (5 questions), energy and fatigue (4 questions), and general concept of health (5 questions). All questions are scored and transformed into a scale ranging from 0 (the worst) to 100 (the best). The scores of these eight domains can be summarized into two main scores of physical and mental components. The examinees filled in the questionnaire individually in the presence of a doctor who was at their disposal in case of difficulties with understanding some questions.

The data were analyzed using the SPSS program, ver. 17. Correlation of the FSS scores with disease duration, EDSS and BDI scores were determined using the Spearman Rank Correlation Test. This included partial correlations to determine the relationship between fatigue and depression severity, adjusting for physical disability, and the relationship between fatigue and EDSS independent of depression severity. Group differences were assessed by Fishers ANOVA, Fishers Exact Probability test and Mann-Whitney U test. A p of value <0.05 was considered statistically significant

RESULTS

The average age of the patients at the time of study was 37.7 ± 8.5 years, where the youngest and oldest patients were 21 and 57, respectively. Out of 120 MS patients, 65% were females and 35% were males. The greatest number of examinees (70%)

were married. Regarding the place of residence, 88.3% lived in town, while the rest (11.7%) lived in the country. An analysis of educational level showed that the majority of the examinees (63.3%) had completed secondary education and were mostly clerks (45%).

Analysis of the course of the disease revealed that most patients had the remittent form of MS (76%) in comparison to secondary progressive (23.3%). The average length of disease was 8.1 ± 5.6, where the minimum and maximum lengths were 1 and 22 years, respectively.

The average value of EDSS score was 3.5 ± 1.8 (range 1-8.0).

The average value of FSS (Krupp's scale) was 4.6 ±1.8, where the minimum and maximum values were 1 and 7, respectively. Based on the FSS score, the patients were divided into a without-fatigue group (MSNF), 23.7% with the score of ≤ 4, and the group with fatigue (MSF), 67.8% and a score higher than 5. The boundary group included 8.5% of patients with the score of 4.1 - 4.9.

The average value of BDI score was 10.7 ± 10.3, with minimum and maximum values of 0 and 39, respectively. Depression was diagnosed in 35% (MSD) of the patients. Depression (BDI>18) was present in 14% of the patients and mild-to-moderate depressive symptoms (BDI 11-17) were found in another 21% patients The level of clinical disability that was evaluated using EDSS, positively correlated to a considerable extent with the severity of fatigue when measured by the FSS scale (rho= 0.480;p =0.000) (Table 1). Fatigue was in poor correlation with the length of disease (p>0.05).

The severity of depression that was evaluated using the Beck scale was in considerable positive correlation with the severity of fatigue when measured by application of the FSS scale (rho 0.572; p = 0.000) (Table 1; Graph 2). The severity of depression was also in correlation with the level of disability (EDSS) (rho=0.265;p= 0.04)

Table 1. Correlation between FSS and clinical parameters

Spearman Rank correlation	
FSS	**Rho (P value)**
Disease duration	0.096(p=0.459)
EDSS	0.480 (p=0.000)
Beck Depression Inventory	0.572 (p=0.000)

The first domain of questionnaire Sf-36, physical health, included the scale of physical functioning (10 questions) which determines limitations of physical activities due to health status. The mean value of physical functioning was 53.3± 33.8. The mean value of limitation due to physical health, i.e. the second domain of the SF-36 questionnaire, consisting of four questions concerning the impact of physical health on everyday activities, was 50.42± 41. Physical pain was evaluated by two questions regarding its intensity and impact on normal performance of home and outside activities. The mean value of physical pain was 62.3 ± 30.0. Vitality and energy were examined using four questions that include the estimation of the feeling of exhaustion, fatigue, enthusiasm and the level of life energy. The mean value of vitality and energy was 49.5 ± 24.7. Social functioning includes two questions referring to the impact of physical and emotional health on normal social activities. In our patients, the mean value was 53.8 ± 24.8. The emotional role included three questions that evaluated the limitations in performance of activities due to emotional problems. It showed mean values of 65.1 ± 29.4. Mental health (mean values 64.4 ± 43.2) was evaluated by five questions that included the presence of neurosis, consternation, melancholy, fatigue, or happiness, as well as the period of the examinees feelings. General health also included five questions referring to the MS patients' self-estimation of current health and their opinion on the accuracy of certain statements about resistance to disease, health prognosis and judgment on current health status, with mean values 62.5 ± 25.7.

Total quality of life was considerably damaged in patients with multiple sclerosis and was considerably poorer in the patients with the secondary

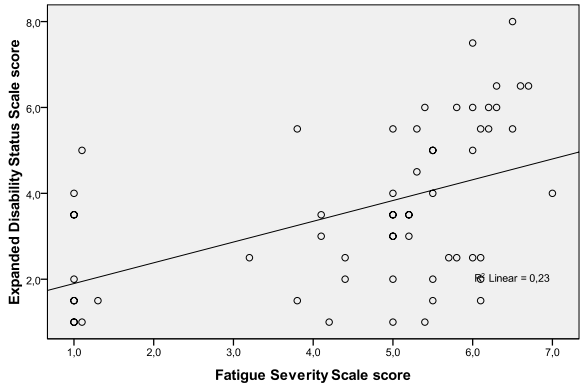

Fig. 1. Correlation between fatique and neurologic disability in MS patients

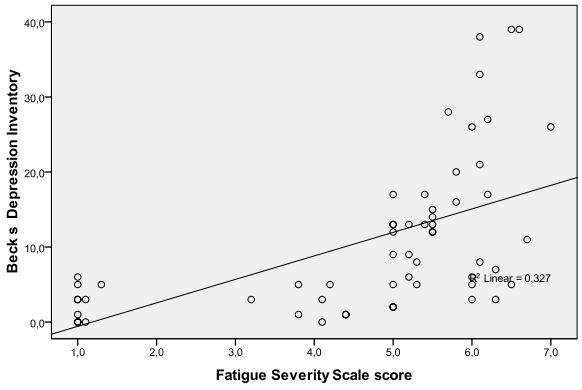

Fig. 2. Correlation between fatique and depression in MS patients

progressive form in comparison to the patients with the relapsing-remittent form (p=0.04)**.** Multivariate regression analysis showed that a higher EDSS score was considerably associated with a lower total score of life quality (rho=-0.696;p=0.000). Physical disability was significantly negatively correlated with the majority of total physical health scores (rho=-0.732;p=0.000) and total mental health scores (rho=-0.572;p=0.000).

Fatigue has a considerable impact on life quality. Patients with fatigue (MSF) have a lower life quality score (37.7±18.8) in comparison to those without fatigue (MSNF) 73.8±20.6 (p=0.000). Multivariate regression analysis showed that fatigue was considerably independently associated with the impaired quality of life.

Depression considerably impairs the quality of life (QOL). The patients with depression (MSD) have a considerably lower QOL score 40.7±21.7 in comparison to those without depression (MSND) 74.0±20.6 (p=0000). Having excluded physical disability and fatigue, we found that depression had a considerable impact on the quality of life using multivariate regression analysis.

DISCUSSION

The obtained results reveal a high percentage of patients (57%) with fatigue, while 14% had clinically significant depression. According to its origin, fatigue may be primary, appearing due to processes in the central nervous system (demyelination, axonal loss, or immune activation) or secondary, due to the impact of depression, sleep disturbance and drug use. In some patients, the symptoms of both fatigue and depression may independently coexist (Bakshi et al., 2003, Kos et al.,2008).

Previous studies that followed fatigue in MS patients and its relation to neurological disability presented contradictory results. In some studies, a positive correlation between fatigue severity and neurological dysfunction was established (Bergamschi et al.,1997) but was not confirmed in others (Bakshi et al., 2000). This study shows that the level of clinical disability, evaluated using the EDSS score, significantly positively correlated with the severity of fatigue measured using the FSS score (rho 0.480; p=0.000).

We have found that the severity of depression when evaluated using the Beck scale of depression, was in considerable positive correlation with the severity of fatigue when evaluated using the FSS scale (rho=0.693;p=0.000). Other authors had contradictory findings. While a number of previously published studies found no association between fatigue and depression (Vercoulen et al.,1996; Moller et al., 1994), the majority of recently published studies found that depression and disability had a signifi-

cant impact on the occurrence of fatigue (Kroencke et al., 2000; Iriarte et al.,2000). In his paper, Bakshi found a significant correlation between FSS and BDI in MS patients, independently of clinical disability (r=0.56;p=0.000) (Bakshi et al., 2000). The lack of association of fatigue and depression may be due to the small sample (Moller et al., 1994), changes in neurobehavioral findings after drug intake (Vercoulen et al.,1996), or use of various scales for fatigue evaluation (Vercoulen et al. 1996). Such findings are surprising if we take into account that the scales for evaluation of depression severity include a section referring to fatigue and sleep disturbance that affects daily fatigue. Some authors suggest the correction of scales for such overlapping (Mohr et al.,1997).

Fatigue and depression often coexist in the same MS patient. The association of fatigue and depression may be explained by the fact that these two entities share mutual mechanisms of origin in MS. These might be psycho-social factors, although specific, pathological lesions of the brain may have a role in MS. Neuron-imaging studies point to the association of depression with T1 hypo-intensive alterations of white brain matter in the frontal, temporal and parietal lobes as well as atrophy of the brain. (Bakshi et al., 2000). This finding leads to the assumption that axonal loss and neuron degeneration in the white matter leads to depression, affecting serotonergic pathways in the cortical-limbic circle that regulates mood. The results of conventional magnetic resonance cannot explain the nature and pathogenesis of fatigue (Filippi et al., 2002). Recent studies, using positron emission tomography (FDG-PET) to explain the nature of fatigue occurrence, pointed to a reduction of glucose metabolism in the bilateral prefrontal cortex and basal ganglia (Roelcke et al., 1997). These areas take part in motor planning, motivation and executive functioning. Considering the mentioned studies, it can be assumed that cortical-subcortical disconnection, i.e. break of limbic and frontal system connection, lies at the basis of fatigue and depression in the same patients. Nevertheless, the impossibility to associate fatigue with MRI lesions of the white matter suggests that the nature of fatigue may rather be explained by the direct capture of cortical and subcortical grey matter than by disconnection. Neuron-imaging studies utilizing functional magnetic resonance support the datum that fatigue is generated in MS by the damage of interaction between the functionally connected cortical and subcortical areas that are responsible for motor planning and execution (Filippi 2002).

This study showed that the level of disability had a considerable negative impact on the quality of life of MS patients (rho=-0.696; p = 0.000). Several studies followed the relation between neurological disability and the effect on life quality of MS patients. The results differed from study to study and ranged from a strong (Henrikson et al., 2001), moderate (Janardhan et al., 2000) to weak (Connor 2001) correlation. Such a great difference among the obtained results may be explained by the exclusion of other factors that affect life quality, such as the effects of fatigue and depression. In the study that followed the effect of clinical disability on the quality of life, Janardhan (2002) showed the considerable association of damaged life quality and mental health, after adjustment of the potential influence of other factors (fatigue, depression).

Our study shows that fatigue and depression have a considerable impact on the quality of life in MS patients, their physical and mental health, i.e. that the patients with fatigue and depression had considerably worse life quality. Previous studies that have followed the life quality of MS patients indicated that patients with secondary progressive MS had a lower score on the scales of life quality in comparison to those with the relapsing-remittent form of MS (Janardhan et al., 2000), and that neurological disability affected the quality of life as well (Janardhan et al., 2000). Recently published studies (Jandardhan 2000) showed that the patients with depression and fatigue had a considerably poorer quality of life, irrespective of physical disability and clinical course of the disease.

In conclusion, this study shows that fatigue and depression independently decrease the quality of life

of MS patients by a considerable extent. Adequate treatment could help the patients and improve the quality of their lives.

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