

Fatigue, Depression and Sleep Disturbances in Iranian Patients with Multiple Sclerosis

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Abstract- Fatigue is one of the most frequent symptoms in patients with multiple sclerosis (MS) and it is difficult to clarify the nature of this symptom and manage it. This study was aimed to evaluate the frequency of fatigue, depression and sleep disturbances in Iranian patients with MS. 100 patients from the outpatient MS clinic of Sina hospital were asked to complete Beck Depression Inventory (BDI), Pittsburg Sleep Quality Index (PSQI), Sleep Disorder Questionnaire (SDQ), Modified Fatigue Impact Scale (MFIS) and Epworth Sleepiness Scale (ESS) questionnaires. Student's t-test, ANOVA, Spearman correlation and Stepwise multiple linear regressions by SPSS version 15.0 were used for data analysis. From participants, 64 had fatigue complaint during day time and 36 did not feel fatigued. BDI, PSQI, MFIS and SDQ scores were significantly higher in fatigued patients than non-fatigued group but there were no statistically significant differences in ESS, EDSS and duration of disease between fatigued and non-fatigued cases. There were significant correlations between MFIS and BDI scores ($r=0.49$, $P=0.01$), MFIS and PSQI scores ($r=0.399$, $P=0.01$) and MFIS and ESS ($r=0.25$, $P=0.01$). This study demonstrates that depression is not the only cause of fatigue in patients with MS and it is also associated with sleep disorders, so this complaint should be carefully evaluated and managed in these patients.

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Introduction

Multiple sclerosis (MS) is the most common inflammatory demyelinating disease of the central nervous system which may lead to a wide range of physical and intellectual disabilities (1,2).

Fatigue is one of the most common symptoms in MS patients, with a reported prevalence of 50% to 90% in these patients (3) MS related fatigue which accompanies with heat and worsens during day time, impacts quality of life of patients (4). Despite amount of studies have been done to clarify MS related fatigue, the exact cause of fatigue in MS is not clear but it may be related to the changes in immune system and nervous system, sleep disturbances, pain and side effects of medications. Fatigue due to demyelination, axonal loss and inflammation is known as primary fatigue, while secondary fatigue is the consequence of depression, infection or sleep disorders (5-7).

Iriarte *et al.* reported the association of fatigue, depression and sleep disturbances in MS patients (8). Ford *et al.* introduced physical and mental part of fatigue by use of fatigue scale and noted the correlation between mental fatigue and depression in MS (9).

Other study illustrated that fatigue is significantly associated with sleep disturbances or abnormality of circadian rhythm that could be unrecognized in MS patients. This problem may disturb routine daily activities that result in decrease in quality of life (10).

Furthermore, depression is the most common mood disorder in MS patients that is reported in about 50% of patients with MS (11,12).

There is no exact reason for depression in MS patients, but temporal lobe lesions and frontal lobe changes are known to be possible causes of depression (13-15).

In some previous studies fatigue is known as a result of depression in MS, but in other studies no relationship

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between MS related fatigue and depression has been reported (16-18).

Sleep disturbances could either be the cause or result of depression in MS patients and both of them might also be associated with fatigue which is frequently seen in these patients. Stanton *et al.* noted fatigue and day time sleepiness in 64% and 32% of MS patients and found anxiety and pain as the most common causes of initial insomnia, and nocturia as the most common cause of middle insomnia (19).

To the best of our knowledge there is so far no study that investigated the relation between fatigue, sleep problems and depression altogether among Iranian MS patients. The upcoming study was therefore designed to identify the role of sleep disturbances and depression in fatigue among Iranian MS patients.

Materials and Methods

Patients

Between September 2008 and September 2009, a total of 100 patients with diagnosis of MS according to McDonald criteria who referred to MS clinic of Sina hospital (Affiliated hospital of Tehran University of Medical Sciences) were included in this cross-sectional study. The study was performed in accordance with principles stated in declaration of Helsinki and was approved by the local ethics committee at Tehran University of Medical Sciences. Upon entrance into the study, all patients signed informed consent to participate in the study.

The exclusion criteria were corticosteroids therapy during the last 2 weeks, anti-depressant medications during last 6 weeks and active MS.

According to fatigue complaint during day time by patients, they were allocated into fatigued and non fatigued groups (3).

Instruments

Demographic data (sex and age), duration of disease, disease course [Relapsing Remitting (RR), Primary Progressive (PP), Secondary Progressive (SP), Progressive Relapsing (PR)], and types of medications were extracted from patients medical files.

After neurological examination, Kurtzke Expanded Disability Status Scale (EDSS) was recorded. All patients answered to instruments including Beck Depression Inventory (BDI), Modified Fatigue Impact Scale (MFIS), Sleep Disorder Questionnaire (SDQ), Pittsburg Sleep Quality Impact scale (PSQI) and Epworth Sleepiness Scale (ESS) questionnaires.

Beck Depression Inventory (BDI) published in 1961 is an instrument for evaluation of depression. Individuals should answer to 21 questions, according to their feelings in the last week. Each answer valued from 0-3 to determine how depressed a person is. Individuals with scores between 0 and 9 are not recognized as depressed, scores between 10 and 18 are indicatives with mild to moderate depression, scores of 19 to 29 values indicate individuals with moderate to severe depression, and scores of 30 to 63 belong to severe depressed cases. Valid Persian version of BDL was applied in our study (20).

Modified Fatigue Impact Scale (MFIS) evaluates fatigue related complications on patient's quality of life. This instrument includes 21 questions. Each question scores between 0 and 4, score of 0 indicates no problem and 4 shows extreme problem. Therefore, the total score of the survey is between 0 and 84, which higher scores indicates greater impairment of the quality of life due to fatigue complaint (3).

The Epworth Sleepiness Scale (ESS), including 8 questions and scoring from 0 to 24 was used to determine sleepiness during daily activities. A score of 10 or more indicates hyper somnolence during daytime (21).

Forty one item sleep disorder questionnaire (SDQ) that evaluates general condition of an individual before sleep, problems during sleep and habit history was answered by our patients (22). For the assessment of sleep quality, valid and reliable Persian version of Pittsburg Sleep Quality Index (PSQI) was used (23).

Using a standard "forward-backward" translation SDQ, ESS and MFIS were translated to Persian. The Persian version of questionnaires administered to 20 MS patients.

The reliability of the questionnaires was assessed by Cronbach's alpha coefficient. Internal consistency reliability was computed by Cronbach's alpha (recommended value $\alpha \geq 0.70$). Content validity was checked by two separate neurologists.

Cronbach's alpha was 0.8 for SDQ, 0.78 for ESS and 0.86 for physical Subscale, 0.84 for cognitive subscale and psychosocial Subscale MFIS.

Statistical analysis

Data analyzed by SPSS version 15.0 software (SPSS Inc, Chicago, Ill). All measurements were tested for deviation from normal distribution applying Kolmogorov-Smirnov test. Quantitative parameters between fatigued and non-fatigued groups were analyzed by Student's t-test and ANOVA. Spearman correlation was performed

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for evaluation of correlation between MFIS, BDI, PSQI and SDQ scores between two groups. Quantitative data presented as mean \pm standard deviation (SD). Stepwise multiple linear regression analyses with MFIS score as dependent variable and the scores of BDI, PSQI, SDQ, ESS, EDSS as independent variables conducted to assess their relevance for fatigue. According to analysis, partial correlations were performed. *P* values less than were 0.05 considered significant.

Results

Seventy five women and twenty five men (F/M=3) with the mean age of 32.5 ± 8.7 and the mean EDSS and duration of disease (year) were 4.8 ± 5.2 and 4.8 ± 5.2 .

Sixty four (64%) patients had fatigue complaint during day time. Mean MFIS, BDI and PSQI scores of all participants were 29.5 ± 18.8 , 14.03 ± 9.4 and 8.4 ± 6.3 , respectively.

Nine patients presented with Primary Progressive (9%), seventy three with Relapsing Remitting, seventeen with Secondary Progressive and one with Progressive Relapsing type of multiple sclerosis.

Based on the results of the study, the ESS score lacked statistical significance comparing the results from fatigued and non-fatigued groups but there were significant differences in the BDI, PSQI, MFIS and SDQ scores (Table 1).

Patients were divided into 4 groups due to duration of disease, then EDSS, MFIS, BDI, PSQI, ESS and SDQ scores were compared among these groups (Table 2).

EDSS score was significantly different in patients with long duration of disease.

In fatigued group, 14 patients were not depressed, 28 had mild to moderate depression, 18 presented with moderate to severe depression and 4 were severely depressed.

Table 1. Comparison of demographic characteristics and scores of questionnaires between fatigued and non-fatigued groups.

Groups	Fatigued	Non-fatigued	<i>P</i> value
Number of cases	64	36	
F/M	47:17=2.7	28:8=3.5	0.63
Married/single.	42:22	21:15	
Age	34.03 ± 8.4	28.4 ± 8.3	0.002
Disease duration	5.4 ± 4.8	4.2 ± 5.7	NS
EDSS	2.8 ± 2.05	2.2 ± 1.6	NS
MFIS	35.3 ± 17.6	19.1 ± 16.5	0.001
PSQI	9.8 ± 6.5	6.05 ± 5.07	0.002
BDI	15.8 ± 8.8	10.7 ± 9.6	0.008
Sleep disorder questionnaire	67.6 ± 21.1	58.08 ± 16.9	0.01
ESS	3.8 ± 3.07	3.6 ± 3.1	NS

NS: non-significant

Table 2. Comparison of EDSS, BDI, MFIS, PSQI, ESS and sleep disorder questionnaire scores in patients with different duration of disease.

Duration of MS	1-5 years	6-10 years	>10 years	<i>P</i> value
EDSS	2.1 ± 1.6	3.4 ± 2.1	3.6 ± 2.4	0.01
MFIS	30.1 ± 17.9	34.3 ± 17.9	35.6 ± 22.1	NS
BDI	13.9 ± 9.1	16.1 ± 11.6	15.7 ± 8.8	NS
PSQI	8.6 ± 6.8	8.5 ± 6.1	6.6 ± 4.1	NS
ESS	3.8 ± 3.0	4.3 ± 3.5	3.9 ± 3.1	NS
Sleep disorder questionnaire	65.4 ± 20.6	64.8 ± 20.6	59.2 ± 16.8	NS

NS: non-significant

Forty eight fatigued patients had PSQI more than 4 and four cases had ESS more than 10. In non-fatigued group, seventeen cases had PSQI more than 4 (significant difference between two groups, $P < 0.05$) and two had ESS more than 10 (no statistically significant difference were found between two groups, $P = 0.84$).

Based on results of the study, there was significant correlation between PSQI and MFIS ($r = 0.399$, $P = 0.01$), and we found significant correlation between MFIS and BDI scores ($r = 0.49$, $P = 0.01$) also MFIS and ESS ($r = 0.25$, $P = 0.01$).

In order to determine those variables that interpret most of the variance for MFIS score in our patients, we performed stepwise multiple linear regression analyses. MFIS was considered as dependent variable, while BDI, PSQI, ESS, EDSS and SDQ were set as predictors. Table 4 shows stepwise linear regression model for variables predicting fatigue in our patients. Among sample, SDQ score was the strongest predictor for fatigue, measure accounting for 25% of variance for MFIS. In addition to SDQ, BDI was found to be a predictor for fatigue, explaining additional 9% of variance for MFIS. The ESS was also found to be significant predictor, explained additionally 2% of variance.

Partial correlation was used to explore the relationship between fatigue MFIS and depression, while controlling for scores on SDQ. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity and homoscedasticity. There was a positive, partial correlation between fatigue and depression, controlling for sleep disturbances, ($r = 0.35$, $P < .001$), with high levels of fatigue being associated with higher levels of depression. Also we found positive correlation between MFIS and PSQI as well as MFIS and ESS ($r = 0.39$, $P < .001$ and $r = 0.33$, $P = 0.001$).

Discussion

To the best of our knowledge this is the first study to determine fatigue, depression and sleep disturbances in Iranian patients with MS.

In current study sixty four patients had fatigue complaint and thirty six were not fatigued during day time that confirmed the previous finding (5). The exact cause of MS related fatigue (which is different from the fatigue due to the depression in duration [MS related fatigue lasts only for several hours] and in body temperature during the fatigue phase) is not determined up to now, but Bakshi noted the hypometabolism of

frontal and sub-cortical areas as the cause of MS related fatigue (21) and Kos reported high energy demand of brain due to reorganization of cortex cause of fatigue in MS patients (7).

It is important to differentiate primary fatigue from the secondary fatigue because secondary fatigue is easy to treat. Since fatigue is a subjective complaint and is defined as decreased physical or psychological energy level, an objective tool like Modified Fatigue Impact Scale (MFIS) should be used to measure this complaint. MFIS score was significantly higher in fatigued group while they had higher BDI score and more sleep disturbances.

These results demonstrate that fatigue can be a presenting symptom of depression as secondary fatigue. Penner *et al.* discussed that relationship between depression and MS related fatigue is not easy to know, although fatigue can be a leading symptom of depression, on the other hand it may cause depression by reducing day time activities (24).

Mohr *et al.* found that the treatment of depression reduces fatigue in MS patients (25). Depressed MS patients develop fatigue 3.6 times more than non-depressed ones according to the Alarica *et al.* findings (26).

In this study BDI score was significantly higher in fatigued group than non-fatigued and there was significant correlation between BDI and MFIS scores that was in agreement with previous studies (3,5,27). The results of this study is against the report of Vercoulen *et al.* that declared no significant relation could be found between fatigue and depression in patients with MS (28). Joffe *et al.* did not support relationship between severity of fatigue and depression as well as the genetic basis for MS related depression (29).

Disease duration and status had been considered to have association with fatigue complaint in MS patients (30) but Tchibana *et al.* did not confirm the mentioned association (31). Our results showed no statistically significant differences in duration of disease and EDSS between fatigued and non-fatigued groups but patients with long period of disease had higher EDSS.

Sleep problems due to nocturia, pain, spasm and restless leg syndrome are common in MS that can result in secondary fatigue. One of the most useful instruments for evaluation of sleep quality is Pittsburg sleep quality index (PSQI).

The mean PQSI in our study, for fatigued and non-fatigued groups were 9.8 and 6.05 respectively which was similar to findings by Loebntanz *et al.* (32). These

findings confirmed the results of the previous study that showed a high correlation between fatigue and disrupted sleep (33). In another study decreased sleep efficiency and increased awaking in MS patients discovered (34).

In some cases it is difficult to distinguish between primary fatigue and secondary fatigue caused by sleepiness during the daytime. In our study there was no significant difference between ESS of two groups which was consistent with previous findings (3).

Our findings also suggest that sleep disturbances are the main predictor for variance in MS related fatigue.

In contrast to some studies that have found no relationship between fatigue and depression (4,28), our results show relationship among these factors, even after controlling for sleep disturbances as a possible confounder. However, the observed effect is less than what described by Penner *et al.* (35).

In conclusion this study suggests that fatigue in MS patients can be the result of depression or sleep disturbances but according to cross-sectional design of this study we could not conclude about the causality direction among fatigue and depression in MS patients.

More studies in different settings are needed to define fatigue in large population of MS patients and its relation with disease activity.

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