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Original Article

Fatigue in multiple sclerosis is a diagnostic challenge: A cross-sectional study

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Abstract

Introduction: Multiple sclerosis (MS) is a chronic and unpredictable demyelinating disease of the central nervous system (CNS). While MS is mostly known for muscle weakness, numbness, and pain, but fatigue is the most common complaint of this condition. Despite this fact, MS related fatigue is one of the most misunderstood symptoms.

Methods: A non-interventional study of 100 individuals was conducted in the MS clinic, Tabriz University of Medical Sciences. Patients were divided into groups with and without complaints of fatigue. The course of the disease was determined for all patients. To quantify fatigue, the Modified Fatigue Impact Scale (MFIS) was used. Furthermore, mood disorders, pain, disability, nocturia, insomnia, and spasticity were evaluated among the patients.

Results: Overall, fatigue was diagnosed in 61 through 100 patients. Depression was reported in 23 patients of whom 19 had fatigue ($P=0.015$). 40 patients showed anxiety 33 of which had fatigue ($P>0.001$). 53 patients of whom reported to have pain (76 patients) showed fatigue ($P=0.001$). Insomnia was reported in 27 patients, where 21 of them had fatigue ($P=0.036$). Nocturia was reported in 10 patients, of whom 9 had fatigue ($P=0.047$). Spasticity was detected in 9 patients, all of whom had fatigue ($P=0.012$).

Conclusion: There are several factors directly and indirectly associated with fatigue that are either fatigue-induced, caused by fatigue, or showing a two-way relationship with it. Understanding these links and attempting to reduce them will improve the quality of life for these patients.

Introduction

Multiple sclerosis (MS) is an immune-mediated inflammation of the central nervous system (CNS) and the most common cause of neurological-related disabilities in young people worldwide. Axonal loss and neurodegeneration appear from the beginning of the disease, which are the main leading factors for disability progression.[1] Fatigue is one of the most common and severe complaints among MS patients.[2,3] Young and Mills determined MS-related fatigue in 2007 as "reversible motor and cognitive impairment with reduced motivation and desire to rest, either appearing spontaneously or brought on by mental or physical activity, humidity, acute infection, and food ingestion". These symptoms may happen at any time, but they usually worsen in the afternoon. For MS patients, fatigue can be observed daily, last for years, and become severe more than any premorbid fatigues.[3] Fatigue significantly disfigures the quality of life, work, and interpersonal relationships of a MS patient.

Some MS patients have experienced significant isolated fatigue several years before the diagnosis,[4] and the presence of fatigue at the beginning of the clinically isolated syndrome (CIS) is linked with an increased risk of developing clinically definite MS in the future.[5]

MS patients may suffer from various fatigue types divided into primary and secondary MS-related fatigue. The primary type refers to the fatigue without any apparent cause, and is explicitly observed in MS conditions. Primary MS-related fatigue (peculiar to MS) is not related to the degree of activity, exacerbates by heat or humidity, and worsens in the early afternoon. The pathophysiology of the primary type involves both peripheral (e.g., muscle) and central processes, but there is an unmistakable evidence that significant irregularities are the most crucial part. In particular, an injured voluntary drive toward the descending motor pathway, probably due to the impairment of motor/afferent tracts affecting the

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motor cortex, performs an important function.[6] Another possible pathophysiology of fatigue in MS is over-stimulation of the frontal lobes during motor preparation and exercise performance.[7-10] A significant decline is reported in metabolic activity of bilateral medial and lateral prefrontal cortex, right supplementary motor area, putamen, and premotor cortex in fluorodeoxyglucose - positron emission tomography (FDG-PET) scans of MS patients with fatigue.[11]

A similar functional magnetic resonance imaging (MRI) study detected a reduction in contralateral sensorimotor cortex and thalamus activity during simple motor activities in MS patients with fatigue.[12] Furthermore, some researches showed that cortical atrophy in the gray and the white matter, especially in the pre-central gyrus and central sulcus, was more significant in MS patients with fatigue than in control subjects.[13-15] There is another evidence suggesting that dopamine imbalance and dysfunction of multifaceted circuits connecting the basal ganglia, frontal cortex, and thalamus caused by inflammation and MS lesions probably have a notable role in central fatigue.[16] Compared to the patients who did not experience fatigue, these patients had significantly higher interferon-gamma and tumor necrosis factor-alpha.[17] According to the pathophysiology of MS, it is suggested that oxidative stress, lipid peroxidation, and mitochondrial dysfunction may play a role in the pathogenesis of fatigue in MS patients.[18-20] Another research discovered a connection between MS-related fatigue and dysfunction of the hypothalamic-pituitary-adrenal axis and a higher adrenocorticotropic hormone level.[21] Conversely, secondary MS-related fatigue results from several simultaneous factors related to MS or other comorbidities, including medications (e.g., interferon beta, anticholinergic, and pain medications),[22] mood disorders such as anxiety and depression,[23,24] sleep disorders (e.g., insomnia),[25-27] bladder control dysfunction (e.g., nocturia),[26,27] motor dysfunction (e.g., motor disability and spasticity),[28-30] pain,[31] and other medical consumption of multiple drugs is entirely usual in MS patients, which leads to more fatigue.[32]

The pathophysiological mechanism of MS-related fatigue is too complicated, and, as a result, measurement and scaling instruments are highly diverse.[28,33] Some trials utilized the Modified Fatigue Impact Scale (MFIS) for assessing fatigue.

This study aimed to evaluate the physical, psychological, and cognitive features of MS-related fatigue and factors that impact or are associated with this problem.

Methods

Participants

A non-interventional, cross-sectional study was conducted in the Multiple Sclerosis clinic at Tabriz University of Medical Sciences. A total of 100 individuals with MS, according to the 2017 updated McDonald criteria, aged from 18 to 60 years old, regardless of Expanded Disability Scaling Score (EDSS), were recruited from the Multiple Sclerosis clinic at Tabriz University of Medical Sciences.

The required sample size was calculated using the Cochran formula ($n = Z2\ (1-\propto 2/)\ (1-P)/d2$) with a fatigue prevalence of 50–90% among MS patients[34] and considering a 95% confidence interval. Finally, 100 MS cases were determined to have participated in the study.

The inclusion criteria were clinically definite MS diagnosed cases according to the 2017 updated McDonald criteria, age between 18 and 60 years, disease duration of at least one year, no relapse during the last six months before participation, and an inclination to participate in the study.

The patients were excluded from the study if they had anemia, thyroid disorders, chronic systemic disease, or other medical comorbidities. In addition the patients under the treatment with antidepressants or medications for fatigue e.g. Modafinil or amantadine, and those who had experienced a relapse or steroid therapy during the previous six months were excluded from the study.

Patients were divided into two groups of "with" and "without" complaints of fatigue. The course of the disease, including CIS, relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS), was determined for all patients.

Evaluation of fatigue

A whole MFIS form was completed for all patients. The MFIS is an updated form of the Fatigue Impact Scale according to fatigue-related items of MS patients and was validated for Iranian patients.[35] The MFIS scale is simple to use and concentrates on how MS-related fatigue impacts the quality of daily life. The complete MFIS includes 21 items, while the shortened version only has 5. The shortened version can be utilized for conditions in which time is inadequate, while the full version generates subscales for physical, cognitive, and psychosocial functioning. The total score of the full MFIS is the sum of the 21 items' scores.

Evaluation of anxiety and depression

To evaluate the anxiety and depression level of the participants Hospital Anxiety and Depression Scale (HADS) was filled out for all patients. HADS is a questionnaire form that can detect anxiety, depression, and potential vegetative outcomes. It has been approved to use for medically sick patients and several MS investigations.[36] This self-reported test includes seven anxiety-related questions and seven depression-related questions. Each question is evaluated straightforwardly (0–3), yielding a range of scores ranging from 0 to 21 for each subscale.

Evaluation of other factors

In this study, we asked the patients about any experience

of pain using a Numerical Pain Rating Score. Patients were asked to make three pain ratings, corresponding to current, best, and worst pain experienced over the past six months, and the average of the three ratings was used to represent the patient's level of pain over the previous six months, and the total pain level was scored from 0 to 10. Moreover, symptoms of nocturia and insomnia were evaluated among the participants. Nocturia was characterized by definition of the International Continence Society as "the complaint that the individual has to wake at night one or more times to void, and each void is preceded and followed by sleep",[37] on the other hand, insomnia is defined as difficulty in falling and staying asleep or waking up too early in the morning for more than three months, which interferes with daily living functions.[38] The presence of spasticity and the severity of disability was determined by an expert neurologist blinded to the presence or absence of fatigue. The severity of disability was determined according to the EDSS, which is a method for evaluating neurologic disability in patients with MS and has been scored from 0 to 10 (0 = average and 10 = death due to MS) within eight functional systems.[39]

Results

In the current study, 100 MS patients with an average age of 37.09 ± 8.77 were enrolled, 71 of which (71%) were female. Fatigue was observed in 61 patients (61%). 52 out of 100 patients (52%) suffered from fatigue. While, among the studied population RRMS was the most common type of MS, with 57 patients, PPMS, CIS, and SPMS included 15 (15%), 16 (16%), and 12 patients (12%), respectively. The prevalence of MS in patients by the presence or absence of fatigue is shown in Figure 1.

The physical, cognitive, or psychosocial subscale, and total MFIS score of patients with fatigue are presented in Table 1.

Depression was reported in 23 patients (23%), of whom 19 patients (82.61%) had fatigue ($P = 0.015$). Anxiety was also observed in 40 patients (40%), 33 (82.5%) of which showed fatigue ($P > 0.001$). Although, most patients with self-reported depression or anxiety had fatigue, but the HADS scores of the two groups did not differ significantly.

69.74% (53 patients) of the patients with an experience of pain (76 patients) were reported to show the symptoms of fatigue ($P = 0.001$), that is while all 76 patients, with and without fatigue, had significantly ($P = 0.003$) different numerical pain scores. Insomnia was reported in 27 patients, 21 (77.78%) of whom had fatigue ($P = 0.036$). Nocturia was observed in 10% of the patients, where 9 of them (90%) had fatigue and only 1 patient (10%) did not report fatigue ($P = 0.047$). The number of patients with spasticity was 9, all of whom had fatigue ($P = 0.012$) (Figure 2). The mean EDSS score of patients with and without fatigue was 3.41 ± 2.23, but there was no discernible difference between the two groups ($P = 0.521$). The HADS total score, Numeric Pain Score, and EDSS scores of the patients are shown in Table 2.

Table 1. The physical subscale, cognitive subscale, psychosocial subscale, and total MFIS score of patients with fatigue

	Mean ± SD
Physical subscale	8.44 ± 3.74
Cognitive subscale	2.75 ± 2.47
Psychosocial subscale	1.71 ± 1.33
Total MFIS score	12.52 ± 6.08

SD, standard deviation.

Discussion

This study is focused on the factors related to fatigue in patients with MS. We assessed the presence of fatigue concerning the phenotype of MS and to detect the secondary type fatigue we analyzed the link between fatigue and other clinical problems like depression, anxiety, pain, nocturia, insomnia, spasticity, and disability.

Although, the patients with RRMS showed the highest evidence of fatigue, but only the PPMS patients showed a significant ($P = 0.027$) relationship with this condition, and the other phenotypes, including SPMS, RRMS, and CIS were not significantly associated with fatigue ($P = 0.668$, 0.464, and 0.123, respectively). The reason

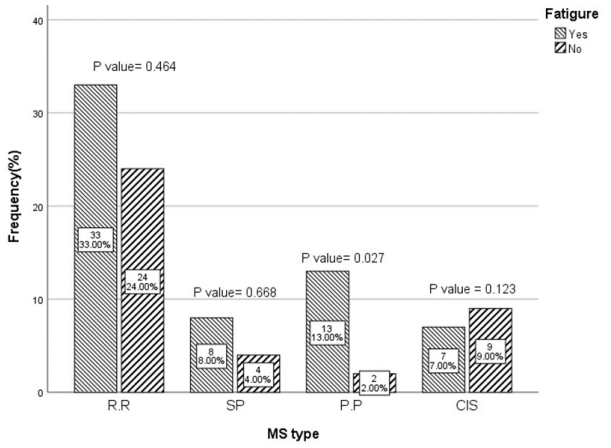

Figure 1. The prevalence of types of MS in patients by the presence or absence of fatigue

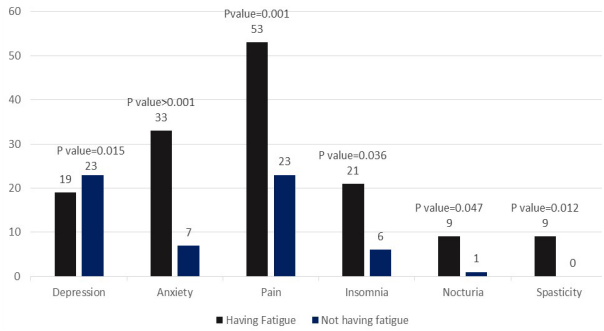

Figure 2. Depression, anxiety, pain, insomnia, nocturia and spasticity in MS patients with and without fatigue

Table 2. HADS total score, numeric pain score and EDSS score in MS patients with and without fatigue

	Having fatigue Mean ± SD	Not having fatigue Mean ± SD	*P* value
HADS total score	10.88 ± 5.07	9.86 ± 7.38	0.429
Numeric pain score	5.15 ± 2.34	3.17 ± 1.23	0.003
EDSS score	3.41 ± 2.23	2.01 ± 2.14	0.521

SD, standard deviation.

for this apparent discrepancy was that a large number of patients (57%) had RRMS. These findings are confirmed by other studies reporting the more prevalent fatigue in progressive MS patrients.[40]

We found that some clinical conditions of MS, including depression, anxiety, insomnia, Nocturia, pain, and spasticity, can be related to fatigue.

Studies have shown that both depression and anxiety are common in MS[38] and are linked to various outcomes like fatigue. There are cross-sectional and longitudinal associations between depression and anxiety and fatigue in MS patients.[41,42] In our study, most MS patients with self-reported depression or/and anxiety had fatigue, but there was no significant difference in the HADS score between patients with and without fatigue. Hence, patients with MS could suffer from fatigue regardless of depression and anxiety.

Although, some studies found a significant association between fatigue and sustained EDSS, reporting that people with moderate to severe fatigue were more likely to experience an exacerbation of sustained EDSS,[43] but in this study, we could not find a significant difference between the EDSS scores of patients with and without fatigue.

We found insomnia to be a more common problem in MS patients with fatigue than those without fatigue. A study by Hare et al, conducted on 114 patients with MS, also showed that patients with more severe insomnia had greater cognitive and physical fatigue.[42] Previous research by Hare et al. suggests insomnia as a highly prevalent complaint amongst people with all medical conditions. Stanton et al showed that the type of insomnia in this disease, associated with severe fatigue, is the type of middle insomnia ($P < 0.001$). Interestingly, the number of days of initial and late insomnia in these patients was not related to the severity of fatigue. This middle insomnia is directly related to daytime fatigue.[26] In another study, Stanton et al examined the causes of different types of insomnia in 60 patients with MS, and concluded that the most typical causes of initial and middle insomnia in these patients are pain and Nocturia, respectively.[26]

In this study, pain was reported by 76% of patients, of whom 69.74% had fatigue, and the numerical pain score was significantly different between patients with and without fatigue. According to various methodological studies, the prevalence of pain in MS patients ranges from 28% to 90%, depending on the methodological study.[44] The pathophysiology of pain in MS is unknown, but it is likely linked to the loss of central afferent and inhibitory pain pathways.[45] Amtmann et al also reported that pain in patients with MS was associated with more significant fatigue.[46] This study also reported a direct relationship between Nocturia and fatigue, where the number of patients with nocturia who had the symptoms of fatigue was more than that for patients without these symptoms. This direct connection can be explained by a study by Stanton et al showing that Nocturia is a common cause of middle insomnia, which is also directly related to daily fatigue.[26] Another study by Bamer et al, investigated 473 patients, and discovered a link between fatigue, sleep problems, and Nocturia.[47] They also reported a substantial link between fatigue and spasticity, which was confirmed by Milinis et al.[48] On the other hand, a study by Karpatkin et al showed that spasticity does not increase due to fatigue.[49] According to our study, we can design an approach to manage fatigue in MS patients (Figure 3). Our study demonstrated a significant correlation between fatigue, insomnia, Nocturia, and spasticity. Therefore, we should manage these factors before treating primary fatigue. While there was a relationship between self-reported anxiety, depression, and fatigue, but no significant difference was observed in the HADS score between patients with and without fatigue. Thus, more studies should be conducted to decide if the HADS score is enough to evaluate the link between mood disorders and fatigue, or not.

Overall, this study focused on factors associated with

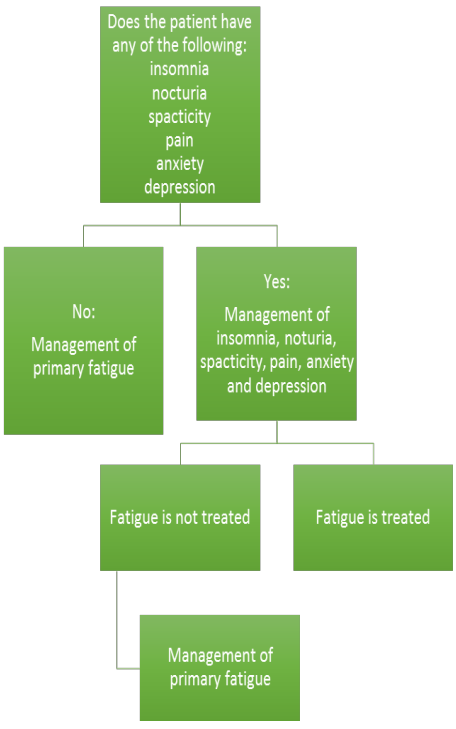

Figure 3. Evaluation of faigue in MS patients

Study Highlights

What is current knowledge?

- Despite the fact that fatigue is the most common symptom of MS, there are many unknowns about it.

What is new here?

- In this study, the factors affecting fatigue in MS disease are mentioned and an algorithm is also presented to evaluate fatigue in these patients.

MS-related fatigue and examined the relationships between depression, anxiety, pain, insomnia, nocturia, and spasticity with fatigue in these patients.

Conclusion

There are still various factors related to fatigue caused by MS, which may be fatigue-induced or in a two-way relationship with fatigue. Therefore, identifying these connections and trying to resolve them will improve the quality of life for MS patients suffering from fatigue.

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Authors' contribution

Conceptualization: Samaneh Hosseini.
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Writing - original draft preparation: Reza Mosaddeghi Heris, Samaneh Hosseini, Sahar Taher.
Writing - review and editing: Reza Mosaddeghi Heris, Sina Hassannezhad.
Resources: Reza Mosaddeghi Heris.
Supervision: Mohammad Yazdchi, Mohammad Ali Sahraian.

Conflict of interest

The writers have no financial or proprietary interests in any of the topics covered in this paper.

Ethical Approval

The study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences (the ethical code was IR.TBZMED.REC.1400.895). All contributors signed written informed consent.

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