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Original Article

Fatigue in A sample of Egyptian Multiple Sclerosis Patients: A Cross Sectional Study

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ABSTRACT

Background: Multiple sclerosis [MS] is an inflammatory demyelinating disease of the central nervous system, which is the second-most common cause of physical handicap in young individuals. Fatigue is the most prevalent [50%–90%] symptom of MS interfering with everyday life with at least one mild symptom of fatigue even in the early stages of the disease [36.5%] when clinical symptoms are still negligible.

The Aim of The Work: To evaluate the prevalence and relation of fatigue in MS patients with sleep disorders and other clinical factors in an attempt to understand the underlying mechanisms of this symptom which might be of help in easing its evaluation and optimizing patient care.

Patients and Methods: A cross-sectional study was performed on patients recruited from MS unit at Al-Azhar University Hospitals in Cairo. Fifty patients were investigated and submitted to clinical evaluation as well as fatigue severity assessment using fatigue severity scale and sleep scales: Epworth sleepiness scale for assessment of daytime sleepiness, Pittsburgh sleep scale for assessment of sleep quality, and polysomnography.

Results: Fatigue was present in 60% of MS patients. Decreased sleep efficiency, pain and progressive types were significantly higher among MS patients with fatigue. Male patients with fatigue were significantly more than those without fatigue. About 84% of patients with MS were complaining from sleep disorder symptoms, 72% had insomnia, pain and nocturia ranged from 54%-60% while leg spasm and narcolepsy were present in 30% and 20% respectively.

Conclusion: The present study emphasized the prevalence of fatigue in MS patients and its relation with sleep disorders and disease progression denoting wide variety of pathological mechanisms and the necessity of multimodal management.

Keywords: Sleep disorders; Polysomnography; Fatigue Scales; Sleep scales.
INTRODUCTION

Multiple sclerosis [MS] is a central nervous system inflammatory demyelinating disease that is the second most common cause of physical disability in young patients [1]. Demyelination, synaptopathy, and neurodegeneration are the pathophysiological hallmarks [2] of the disease. Based on studies using an animal model of MS, immune-mediated processes involving immune cells and soluble cytokines could also lead to excitotoxic changes and neurodegeneration, whereas an immune-mediated attack by blood-borne autoreactive T lymphocytes will determine the incidence of demyelination [3].

Fatigue is the most common symptom [50–90%] of MS that interferes with daily life, with at least one mild symptom of fatigue that will be present in the early stages of the disease [36.5%] when clinical symptoms are still minimal [4]. In fact, the definition of fatigue remains vague. The MS council for clinical practice guidelines has defined it as “a subjective lack of physical or mental energy or both, that is perceived by the individual or caregiver to interfere with the usual and desired activities”. Patients describe it as a difficult symptom that worsens during the day, as well as in hot and humid conditions [2]. MS fatigue is a multi-dimensional symptom with physical, cognitive, and psychosocial aspects, according to scientific bases. Furthermore, the construct can be separated into fatigability, which is objectively evaluated by motor/cognitive task output, and self-reported fatigue, which is measured by a self-administered questionnaire [5].

Since fatigue is a subjective experience, it can only be assessed directly by verbal reports, so it is mainly measured through questionnaires and clinical interviews [6]. In terms of primary factors, a number of studies have looked into the role of central and peripheral inflammatory processes in MS fatigue. The relationship between fatigue and the orexin-A system [7], the hypothalamic-pituitary-adrenal axis [8], and some CSF markers [9, 10] was inconclusive.

Although the available evidence was restricted, serum proinflammatory cytokines [i.e., IL6, TNF, and IFN] appeared to be linked to MS fatigue [5]. Finally, a few data were available on the T-cell population [CD3+, CD4+ T lymphocytes] [11] or regulatory-T cells [12] or peripheral markers of inflammation [CRP, ESR, and soluble ICAM1] [13–19], and such studies failed to find a correlation between MS fatigue and these measures [8].

As indicated by the common finding of exercise intolerance, some MS patients with fatigue may also have features of autonomic dysregulation, such as hypoc-adrerenergic orthostatic response [16].

Neuroimaging studies resulted in plenty of intriguing leads in the search for a connection between MS and fatigue. The majority of early studies that used traditional MRI measures of lesion burden or lesion position found no connection between fatigue ratings and the severity of the lesion [17]. Studies using more sophisticated imaging measures, on the other hand, have found links between fatigue and regional atrophy [18], as well as pathways attaching frontal white matter to the thalamus and basal ganglia [19]. Cortical thickness, disturbance of fronto-parietal white matter lesion burden, and tests of axonal injury using MR spectroscopy are among the other MRI findings linked to self-reported fatigue [20].

Individuals with MS who performed a repetitive motor task had more cortical activity in the frontal and motor areas, while this activity was limited in those who performed a task involving continuous hand grip [21], according to functional MRI studies [22]. The declining performance in MS cases have been related to increased activation in the basal ganglia, frontal areas [superior, medial, middle, and inferior regions], parietal regions [precuneus and cuneus], thalamus, and occipital lobes [23]. Furthermore, the influence of environmental, genetic, and epigenetic MS risk factors on MS fatigue is significant. UV exposure, vitamin D consumption, smoking, dietary, and exercise behaviors, as well as body mass index, are all variables to consider [24].

Controlling some confounders that are common in MS and can affect MS fatigue is also important. Physical impairment [25], mental symptoms [26, 27], and sleep disturbances are among them [28].

AIM OF THE WORK

The aim of this study is to assess fatigue in MS patients and its relation to clinical as well as different contributing factors as pain and sleep disorders in an attempt to improve the understanding of this common symptom as a necessary step for proper management.

SUBJECTS AND METHODS

Study design: A cross-sectional study was carried out at the MS unit of Neurology Department at Al-Azhar University Hospitals [Al Hussein and Bab Al-sharia] during the period from October 2018 to December 2020.

Inclusion criteria: Fifty MS patients and twenty-five healthy volunteers were included in the current study. Those patients were further assorted based on modified McDonald’s Criteria 2017 [29].

Exclusion criteria: 1- Patients with systemic disease
that could affect sleep or cause fatigue as: hepatic failure, renal failure, chest diseases, etc. [30]. 2- Patients who received corticosteroid drugs in the previous 3 months [30], 3- Patients with psychiatric disorders that could affect sleep or fatigue as depression or bipolar disorder, etc. [31].

All participants were subjected to:

1- Full history taking, general and neurological examination. 2- Clinical severity assessment of MS patients using expanded disability status scale [EDSS] [31], 3- Fatigue severity assessment using fatigue severity scale, in which a score of 5 or more was indicative of fatigue [range; 0-17] [38], 4- Sleep scales: Epworth sleepiness scale [ESS] for the assessment of daytime sleepiness, where a score of more than 10 indicating excessive day time sleepiness [32], and Pittsburgh sleep scale [PSC] for the assessment of sleep quality, based on a zero to three scale, in which three reflects the negative extreme on the scale [33]. 5- Polysomnography [PSG]: Full laboratory-based PSG and scoring followed the standards of American Academy of Sleep Medicine 2007 [34, 39].

Ethical approval: The ethical approval has been obtained from Al-Azhar Faculty of Medicine's local ethical committees in Cairo. Prior to enrollment in the trial, written informed consents of the participants were obtained. Using a unique code number for each patient, privacy and confidentiality was preserved throughout the study process.

Statistical analysis of data: The SPSS computer package version 25.0 [IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp., USA] was used. For quantitative data, the mean and standard deviation SD were utilized, while for qualitative variables, the frequency and percentage were employed. The Mann-Whitney test was used to analyze differences in means of quantitative non-parametric variables, whereas the Chi-square test or Fisher's Exact test was used to analyze variations in frequency of qualitative variables. The statistical methods were checked using a p<0.05 significance level.

Table 1: Clinical characteristics of multiple sclerosis among cases

| Variables                        | Cases (n, %) |
|----------------------------------|-------------|
| Type of MS                        |             |
| RRMS                             | 17 [34.0]   |
| PPMS                             | 6 [12.0]    |
| SPMS                             | 27 [54.0]   |
| Expanded disability status scale |             |
| Mean ± SD; Min – Max             | 3.8 ± 1.6; 1.5 – 6.5 |
| Mini mental state                |             |
| Mean ± SD; Min – Max             | 29.1 ± 0.9; 27 – 30 |
| Sensory symptoms                 | 29 [58.0]   |
| Motor symptoms                   | 25 [50.0]   |
| Ataxia                           | 6 [12.0]    |
| Optic neuritis                   | 6 [12.0]    |
| Trigeminal neuralgia             | 2 [4.0]     |
| Facial weakness                  | 2 [4.0]     |

RESULTS

The study comprised 50 MS patients with a mean age of 28.4 ± 8.0 years, ranging from 18 to 45 years, 64 percent of whom were females, a mean illness duration of 5.2 ± 2.6 years, a mean age of disease onset of 26.6 ± 6.4 years, and a mean BMI of 23.9 ± 3.2 [kg/m2] ranging from 16 to 29 years [Figure 1].

The most common type of MS was SPMS [54%] followed by RRMS [34%] and PPMS [12%], the mean expanded disability status scale [EDSS] was 3.8 ± 1.6, the mean mini mental state was 29.1 ± 0.9 and sensory symptoms were prevalent in 58% of patients. Half of the patients had motor symptoms; ataxia and optic neuritis were present in 12% for each and the least prevalent symptoms were trigeminal neuralgia and facial weakness, 4% for each [Table 1].

Both Pittsburgh and Epworth sleepiness scales were significantly higher [P<0.001] among cases with MS compared to controls [Figure 2].

PSG parameters among MS cases showed significant increases in stages N1% and N2%, periodic limb movement, and respiratory disturbance index showed significant decrease in both sleep efficiency and REM percentage when compared with controls [Table 2].

Regarding sleep- related disorders, 84% of patients with MS complained from sleeping disorders symptoms, 72% had insomnia, pain and nocturia ranged from 54%-60% while leg spasms and narcolepsy were present in 30% and 20%, respectively [Figure 3]. Thirty patients [60%] had fatigue. Fatigue was significantly evident among males with MS. Decreased sleep efficiency, pain and progressive types of MS were significantly higher among patients with fatigue. Other variables did not show significant differences when stratified by fatigue [Table 3].
Values present as mean ± SD were analyzed by Mann-Whitney U test. *: Significant.

Table [2]: Polysomnography parameters among the study samples

| Variables                          | Cases Mean ± SD | Control Mean ± SD | P-value |
|------------------------------------|-----------------|-------------------|---------|
| Sleep latency                      | 23.4 ± 18.8; 2 – 65 | 19.7 ± 4.4; 12 – 26 | 0.362   |
| Sleep efficiency %                 | 67.6 ± 20.6; 19 – 95 | 87.0 ± 4.1; 81 – 95 | <0.001* |
| Stage N1%                          | 10.5 ± 5.4; 2 – 22 | 5.8 ± 2.8; 1 – 10  | <0.001* |
| Stage N2%                          | 54.9 ± 5.3; 40 – 64 | 50.2 ± 3.3; 45 – 56 | <0.001* |
| Stage N3%                          | 18.0 ± 5.6; 5 – 30 | 20.0 ± 1.4; 18 – 22 | 0.088   |
| REM latency [min]                  | 61.5 ± 40.8; 10 – 142 | 64.4 ± 5.4; 51 – 73 | 0.726   |
| REM%                               | 17.3 ± 5.5; 5 – 33  | 23.6 ± 3.4; 19 – 30 | <0.001* |
| Periodic limb movement             | 4.8 ± 5.0; 0 – 18   | 1.4 ± 1.0; 0.5 – 5  | 0.001*  |
| Respiratory disturbance index      | 7.1 ± 8.1; 0 – 31   | 0.4 ± 0.3; 0 – 0.9  | <0.001* |

Table [3]: Relation of fatigue with different study variables among cases with multiple sclerosis

| Variables                          | Fatigue [n=30] Mean ± SD | No fatigue [n=20] Mean ± SD | P-value |
|------------------------------------|---------------------------|----------------------------|---------|
| Age [years]                        | 28.0 ± 8.4                | 29.0 ± 7.6                 | 0.481   |
| Sex [h, %]                         | Male 15 [50.0]            | 3 [15.0]                   | 0.016*  |
|                                  | Female 15 [50.0]          | 17 [85.0]                  |         |
| BMI [kg/m²]                        | 23.5 ± 3.2                | 24.4 ± 3.2                 | 0.467   |
| Mini mental state                 | 29.0 ± 1.0                | 29.3 ± 0.8                 | 0.265   |
| Duration of illness [years]       | 5.5 ± 2.4                 | 4.9 ± 3.0                  | 0.196   |
| Age of onset [years]              | 26.6 ± 6.9                | 26.6 ± 5.6                 | 0.897   |
| Pittsburgh scale                  | 9.1 ± 4.7                 | 11.6 ± 5.0                 | 0.141   |
| Epworth sleepiness scale          | 9.7 ± 6.7                 | 8.9 ± 6.8                  | 0.571   |
| Sleep latency                     | 19.7 ± 15.4               | 28.9 ± 22.3                | 0.117   |
| Sleep efficiency %                | 75.7 ± 12.0               | 55.3 ± 24.8                | 0.002*  |
| Stage N1%                         | 9.7 ± 5.1                 | 11.8 ± 5.8                 | 0.261   |
| Stage N2%                         | 54.5 ± 5.1                | 55.6 ± 5.8                 | 0.374   |
| Stage N3%                         | 17.8 ± 5.2                | 18.4 ± 6.2                 | 0.850   |
| REM latency [min]                 | 55.5 ± 40.0               | 70.5 ± 41.4                | 0.168   |
| REM%                               | 18.3 ± 5.8                | 15.7 ± 4.7                 | 0.127   |
| Periodic limb movement            | 4.5 ± 5.8                 | 5.3 ± 3.7                  | 0.571   |
| Respiratory disturbance index     | 8.2 ± 9.7                 | 5.5 ± 4.7                  | 0.937   |
| Expanded disability status scale  | 3.7 ± 1.6                 | 3.9 ± 1.5                  | 0.617   |
| Insomnia [positive]               | 21 [70.0]                 | 15 [75.0]                  | 0.758   |
| Sleep disorder symptoms           | 24 [80.0]                 | 18 [90.0]                  | 0.450   |
| Pain                              | 22 [73.3]                 | 5 [25.0]                   | 0.001*  |
| Leg spasm                         | 10 [33.3]                 | 5 [25.0]                   | 0.754   |
| Nocturia                          | 19 [63.3]                 | 11 [55.0]                  | 0.572   |
| Hypersomnolence                   | 16 [53.3]                 | 5 [25.0]                   | 0.079   |
| Narcolepsy                        | 6 [20.0]                  | 4 [20.0]                   | 1.000   |
| Types of MS                       | RRMS 7 [23.3]             | 10 [50.0]                  | 0.037*  |
|                                  | PPMS 6 [20.0]             | 0 [0.0]                    |         |
|                                  | SPMS 17 [56.7]            | 10 [50.0]                  |         |
| Sensory symptoms                  | 20 [66.7]                 | 9 [45.0]                   | 0.154   |
| Motor symptoms                    | 13 [43.3]                 | 12 [60.0]                  | 0.387   |
| Ataxia                            | 5 [16.7]                  | 1 [5.0]                    | 0.381   |
| Optic neuritis                    | 3 [10.0]                  | 3 [15.0]                   | 0.672   |
| Trigeminal neuralgia              | 1 [3.3]                   | 1 [5.0]                    | 1.000   |
| Facial weakness                   | 1 [3.3]                   | 1 [5.0]                    | 1.000   |

Values present as number & % were analyzed by Fisher’s Exact or Chi-square tests. Values present as mean ± SD were analyzed by Mann-Whitney U test. *: Significant.
Figure [1]: Demographic characteristics of multiple sclerosis among cases.

Figure [2]: Sleep related scales among the study samples.

Figure [3]: Sleep-related disorders among cases with multiple sclerosis


Discussion

Individuals with MS can clearly differentiate their fatigue from feelings of weakness or emotional feelings of depression or listlessness [36], an observation stated in this study by the non-significant statistical difference between patients with and without fatigue regarding sleep quality and daytime sleepiness screened for by Pittsburgh and Epworth sleepiness scales respectively. The most prevalent symptom of MS is subjective fatigue [reported by more than 80 percent of patients in some studies [37], but only 60 percent in this study]. This could be due to variances in clinical features and other factors that contribute to fatigue, as well as the scales employed in different research. Fatigue occurs across all clinical subtypes of multiple sclerosis (MS) [38-40]. Patients with secondary progressive disease, on the other hand, may be at the greatest risk. Relapses, the accumulation of impairment and, in particular, the loss of ambulation; all raise the likelihood of fatigue [40, 41]. Fatigue has been connected to the severity of disease and the overall severity of neurological impairment, but not to the duration of the condition [40]. This supports our findings as we did not find a significant difference between fatigued and non-fatigued patients regarding the duration of illness. Another contradiction was observed with clinical severity measured by EDSS which can be explained by the less severe cases in this study and the minority of patients with high EDSS scores.

The results of this study are matching with the mentioned studies regarding disease progression. In some research, cognitive impairment has been shown to be a risk factor for fatigue in MS [42, 43]; however there was no statistically significant difference between patients with and without fatigue in this study regarding cognition, which was assessed using the Mini Mental State Examination. This can be explained by the differences in fatigue definitions and assessments, as this study only employed the fatigue severity scale, which is primarily concerned with physical rather than cognitive domains. Although this conclusion has not been consistent [42, 43], age does not appear to be highly connected to fatigue in our study. Gender variations do not appear to be significant in fatigue frequency [42, 43] while, in our study, fatigue was significantly higher among males which may be explained by the more severe and progressive nature of MS in males than in females. Fatigue has a significant impact on people with MS, as it can affect all aspects of daily functioning and significantly reduce quality of life [38, 44, 45]. Studies have connected weariness to early retirement and unemployment [42, 46, 47]. Furthermore, there appears to be a relation between fatigue and sleep disturbances in MS in this study as well as another study [49], since sleep disturbances and disorders are widespread in MS patients [49]. Consistent with our findings, insomnia, sleep apnea, nocturia, periodic leg movements of sleep, and restless legs syndrome were all found to be more common in people with MS compared to healthy controls [49]. MS patients with severe fatigue were shown in some studies to have more than twice as many sleep disorders as those with little or no fatigue [50]. In this study, sleep respiratory disturbance was not significantly linked to fatigue which was the strongest factor in other studies [49, 51], differing, to some extent, with the present study. Overall, the link between sleep disorders and fatigue was not very significant which may be explained by the difference in other clinical factors, severity of the condition as well as the only focused physical domain of fatigue in this study. Fatigue is linked to pain in MS, according to this study as well as other studies. Muscle spasms and neuralgias are common causes of pain in MS patients. Pain can enhance tiredness and contribute to deconditioning, which can increase functional deficits [59].

Study limitations: First: Most cases were not very severe, so the relation of study variables with disease severity may not be totally confirmed. Second: The distribution of clinical types of MS was not as that of the common types in general population [generally RRMS is the most common]. Third: Only physical domain has been assessed in this study, while other fatigue domains have not been subjected to assessment. Fourth: The effect of different drugs of disease-modifying therapy used by the participant patients may affect fatigue either positively or negatively.

Conclusions: Fatigue is a common symptom in MS, which may be underestimated. It is also related to several factors and has numerous economic and psychosocial hazards, so should it be carefully searched for and properly studied for better management.

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