Study of fatigue frequency and its association with sociodemographic and clinical variables in patients with multiple sclerosis

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ABSTRACT

الأهداف: تقييم تكرار التعب وعلاقته مع المتغيرات الديموغرافية ومتغيرات المرض الخاصة في المرضى المصابين بالتصلب المتعدد.

الطريقة: اشتملت هذه الدراسة على 300 مريض (72% أنثى، 28% ذكر) تم تشخيصهم بالتصلب المتعدد راجعوا العيادات الخارجية للتصلب المتعدد لمستشفى الإمام رضا، التابع لجامعة كرمنشاه للعلوم الطبية، كرمنشاه، إيران. كما تم تقيمهم خلال الفترة من نوفمبر 2011م حتى ديسمبر 2012م. تم أخذ المتغيرات الديموغرافية والسريرية باستبيان معد. كما تم قياس التعب باستخدام مقياس شدة التعب.

النتائج: كانت نسبة تكرار 62.3% ومعدل أعمار المرضى 35.26±8.7، بينما معدل أعمار المرضى المصابين بالتعب 36.51±8.65. ظهر التعب لدى جميع المرضى بشكل متطور للمرض و 54.8% من مرضى التصلب المتعدد الذين ظهرت لديهم النكسة.

خاتمة: يعد التعب من الأعراض المتكررة في مرضى التصلب المتعدد ومتلازم من نوع المرض، ومضاد الفيروسات، والجنس، ومدة المرض. لم تظهر هنالك أي علاقة بين التعب، والعمر، ومستوى التعليم، والحالة الإجتماعية، من الضروري تسليط الضوء على أهمية مرض التصلب المتعدد واستخدام أدوات كمية لتقييمه.

Objective: To evaluate the frequency of fatigue and its association with demographic variables and disease specific variables in multiple sclerosis (MS) patients.

Methods: In this study, 300 patients (72% female, 28% male) with clinically definite MS admitted to the outpatient MS clinic of Imam Reza Hospital, affiliated to Kermanshah University of Medical Sciences, Kermanshah, Iran, were evaluated between November 2011 and September 2012. Their demographic and clinical characteristics were recorded on standardized forms. Fatigue was assessed using the fatigue severity scale.

Results: The frequency of fatigue was 62.3%, the mean age of patients was 35.26±8.7 SD. The mean age of fatigued patients was 36.51±8.65 SD. Fatigue was found in 100% of progressive forms of disease, and 54.8% of relapsing-remitting MS patients.

Conclusion: Fatigue was a frequent sign in studied MS patients, and was associated with type of disease, interferon, gender, and duration of disease. There was no association between fatigue and age, education, and marital state. It is important to pay more attention to fatigue in MS patients, and use quantitative tools for its assessment.

Neurosciences 2014; Vol. 19 (1): 38-42

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Received 22nd August 2013. Accepted 11th November 2013.

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Multiple sclerosis (MS) is one of the most frequent disorders of the CNS in young adults. Fatigue is one of the disabling signs of this disease, and is reported to interfere with a patient's daily functioning.[1] Fatigue appears to be multi-factorial; however, the causes of fatigue in patients with MS are unknown. There is some indication that primary fatigue results directly

Disclosure. The authors declare no conflicting interests, support or funding from any drug company.

from the MS disease process, such as demyelinization, inflammation, and axonal loss in the CNS.[2,3] Primary fatigue may be secondary to immune factors,[2,3] asthenia,[4] and spasticity due to pyramidal-tract involvement.[4] Non primary fatigue results from situations such as sleep problems, deconditioning, depression, and other psychological factors, such as feelings of hopelessness, and reduced feelings of self-efficacy.[3] Personal factors such as age, socioeconomic status, race, and gender influence the presence and experience of fatigue.[5] There is a need to identify variables that may affect fatigue in patients with MS. In this study, we aim to determine the relationship between fatigue, sociodemographic, and clinical variables in a population of patients with MS.

Methods. Patients with clinically definite MS admitted to the outpatient MS clinic of Imam Reza Hospital, affiliated to Kermanshah University of Medical Sciences, Kermanshah, Iran, between November 2011 and September 2012 were included in this study. All the patients with MS were diagnosed according to the 2005 McDonald's criteria.[6] Informed consent was obtained from all the patients, and Kermanshah University of Medical Sciences approved the study protocol. Patients with hypothyroidism, chronic anemia, chronic hepatitis, diabetes mellitus, heart failure, malignancies, and other chronic systemic disease, or those taking psychoactive medications in the past 2 months that might affect fatigue (for example steroids, amantadine, or antidepressants) were excluded from the study. Over the 2-year study period, we prospectively interviewed and examined patients for the presence of fatigue. Fatigue was defined as an abnormal sense of tiredness or lack of energy out of proportion to the degree of daily effort or degree of disability. Fatigue symptoms were quantified using the Fatigue Severity Scale (FSS) - a 9-statement interview, from which an average score is determined on a 7-point scale.[7] The scale addresses fatigue's effects on daily functioning, querying its relationship to motivation, physical activity, work, family, and social life, and asking respondents to rate the ease with which they are fatigued, and the degree to which the symptom poses a problem for them. This scale shows sensitivity, reliability, and internal consistency in the assessment of fatigue.[7] Patients were asked to represent their fatigue during the preceding 2 months when responding to the interview. Based on the FSS scores, patients were divided in 2 groups: MS with fatigue with an FSS score of 5.0 or more, and MS without fatigue with an FSS of 4.0 or less. Patients with FSS scores between 4.1-4.9 were felt to have borderline fatigue, and thus were not placed into the group analysis. The demographic and clinical characteristics of the MS patients were recorded on standardized forms. The Statistical Package for Social Sciences version 16 (SPSS Inc., Chicago, IL, USA) was used to perform all statistical calculations. Continuous variables were expressed as mean values±SD, and categorical variables as percentages. Categorical variables were compared by Pearson chi-square test. A p-value <0.05 was considered statistically significant for all tests.

Results. A total of 320 patients with MS were included in the study, and 20 subjects dropped out.

Table 1 - Demographic and multiple sclerosis (MS) characteristics of study sample (n=300).

Characteristics	No. (%)	
Gender		
Male	84	(28.0)
Female	216	(72.0)
Age subgroup		
<17	3	(1.0)
17-35	165	(55.0)
35-50	122	(40.7)
>50	10	(3.3)
Education level		
Uneducated	6	(2.0)
<Diploma	74	(24.7)
Diploma	127	(42.3)
Academic degree	93	(31.0)
MS subtype		
Relapsing-remitting	250	(83.4)
Relapsing-progressive	13	(4.3)
Secondary progressive	24	(8.0)
Primary progressive	13	(4.3)
Disease duration (year, mean)	7.28±5.79	
Interferon treatment		
Yes	244	(81.3)
No	56	(18.7)
Interferon type		
CinnoVex	211	(86.5)
ReciGen	5	(2.0)
Rebif	9	(3.7)
Betaferon	10	(4.0)
Avonex	9	(3.7)
Marital status		
Single	111	(37.0)
Married	189	(63.0)
Work situation		
Unemployed, student, housewife	236	(78.7)
Employed	45	(15.0)
Retired	19	(6.3)

Eighty-four (28%) of the patients were males, and 216 (72%) were females. The patients' mean age was 35.26±8.73 years; mean disease duration was 7.28±5.79 years. Two hundred and fifty (83.4%) of the patients had a relapsing-remitting course, and 50 (16.6%) had a progressive course. The prevalence of fatigue in this population was 62.3%. The demographic and clinical characteristics of the MS patients are shown in **Table 1**. Fatigue was associated with the clinical course of MS. On comparison of the MS type, the group with progressive MS generally experienced greater problems compared with the group with relapsing-remitting MS (p=0.00) (**Table 2**).

Two hundred and forty-four (81.3%) patients used beta interferon. Nine used interferon beta-1a (Avonex®, Biogen Idec, Boston, MA, USA), 10 used interferon beta-1b (Betaferon®, Schering Inc., Berlin, Germany), and 211 used interferon beta-1a (CinnoVex®, CinnaGen Co, Tehran, Iran), 9 used interferon beta-1a (Rebif®, Merck Sereno, Geneva, Switzerland), 5 used interferon beta-1a (ReciGen®, CinnaGen Co, Tehran, Iran). Fatigue was present in 162 of 244 interferon treated patients compared to 25 of the 56 patients not treated

Table 2 - Demographics and disease characteristics in multiple sclerosis (MS) patients with fatigue (MSPF) versus MS patients without fatigue (MSPWF).

Characteristics	MSPF	MSPWF	*P*-value
	No. (%)		
Gender			
Male	60 (71.4)	24 (28.6)	0.043
Female	127 (58.8)	89 (41.2)	
Age subgroup			
<17	1 (33.3)	2 (66.7)	
17-35	93 (56.4)	72 (43.6)	0.052
35-50	85 (69.7)	37 (30.3)	
>50	8 (80.0)	2 (20.0)	
Education level			
Uneducated	3 (50.0)	3 (50.0)	
<Diploma	57 (77.0)	17 (23.0)	0.083
Diploma	75 (59.1)	52 (40.9)	
Academic degree	52 (55.0)	41 (44.1)	
MS subtype			
Relapsing-remitting	137 (54.8)	113 (45.2)	
Relapsing-progressive	13 (100)	0 -	0.00
Secondary progressive	24 (100)	0 -	
Primary progressive	13 (100)	0 -	
Disease duration (year, mean)	8.09±6.32	5.94±4.50	0.001
Interferon treatment			
Yes	162 (66.4)	82 (33.6)	0.002
No	25 (44.6)	31 (55.4)	
Interferon type			
CinnoVex	144 (68.2)	67 (31.8)	
ReciGen	1 (20.0)	4 (80.0)	
Rebif	7 (77.8)	2 (22.2)	0.002
Betaferon	5 (50.0)	5 (50.0)	
Avonex	5 (55.6)	4 (44.4)	
Marital status			
Single	64 (65.4)	47 (34.6)	0.483
Married	123 (65.1)	66 (34.9)	
Work situation			
Unemployed, student, housewife	142 (60.2)	94 (39.8)	
Employed	30 (66.7)	15 (33.3)	0.025
Retired	15 (78.9)	4 (21.1)	

with interferon (p=0.002). The mean treatment duration with interferon was higher in MS patients with fatigue, and the difference was statistically significant (p=0.029). The mean disease duration was higher in MS patients who experienced fatigue compared to non-fatigue MS patients (8.09±6.32 versus 5.94±4.50; p=0.001). Two percent of the patients were uneducated, 27.7% were less than high school diploma level educated, 42.3% had a high school diploma, and 31% of the patients had academic degrees. There was no meaningful association between fatigue and educational level (p=0.083), **Table 2**. There was no statistically significant difference in mean age between fatigued and non-fatigued patients (36.51±8.65 versus 33.19±8.49; p=0.052), 58.8% of the female patients, and 71.4% of males experienced fatigue (p=0.043). Marital status was not significantly associated with fatigue. Fatigue was present in 64 (65.4%) of the single patients, and in 123 (65.1%) of the married patients (p=0.483).

Discussion. Fatigue exists in approximately 20% of patients evaluated in primary care clinics,[8] while 96% of MS patients experience fatigue, 88% of whom report fatigue as one of the disabling signs of the disease.[1,9] Our results indicate that fatigue is one of the most common complaints of patients with MS, and are in accordance with previous findings.[10-14]

Our study found that there was no significant relationship between fatigue and age in MS patients (p=0.052). One study found a possible positive association between fatigue and age,[15] while others found that no such association exists.[4,15-18] Our results showed higher ratings for fatigue on the FSS in male patients compared with female patients (p=0.043). One explanation is that the progressive MS subtype was higher in male patients (29 patients of 84). However, previous studies have shown no significant association between gender and fatigue in MS.[4,10,11,15,17,19-21] In the present study, there was no significant association between fatigue and marital status (p=0.483), and these results are consistent with several past studies.[21] The relationship between fatigue and educational level was also not significant (p=0.083). However, in one study, education level was found to be negatively associated with fatigue.[15]

Our results showed that fatigue frequency was higher in patients with the progressive subtype versus RR patients (p=0.000), again consistent with findings of most of the previous studies.[10,18,22-24] Patients with relapsing-remitting MS may experience fatigue as well as those with the primary progressive form.[18,25] Disability, on the other hand, may be a predicting factor of fatigue, although the results of studies on this factor differ. Forbes and associates[25] found that patients in the different diagnosis subtypes, with more severe disease and disability scored higher on the fatigue scale. Likewise, Kroencke et al[18] showed that disability was a significant predictor of fatigue. In contrast, 2 other studies[17,19] found no association between severity of disability and fatigue experience. In the current study, there was a significant association between fatigue and disease duration (p=0.001). Four studies[4,16,18,20] found that duration of illness was not associated with the likelihood of experiencing fatigue, while 2 studies found a possible association between duration of illness and fatigue.[14,15] Our study also showed that fatigue frequency was higher in MS patients who were under treatment with interferon compared to non-interferon treated patients (p=0.001). Similarly, other studies indicate that fatigue may be a side effect of interferon treatment.[4,26-28]

Our study limitations include: small sample size, lack of a healthy control group in order to compare the frequency of the fatigue, no consideration of other factors that may affect fatigue such as disease disability, exercise habits of the patients, the number of tasks at home or work. Further studies examining different aspects of fatigue are recommended.

In conclusion, fatigue was a frequent sign in MS patients and was associated with type of disease, interferon, gender, and duration of disease. There was no association between fatigue and age, education, and marital state. It is important to pay more attention to fatigue in MS patients, and use quantitative tools for its assessment.

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ETHICAL CONSENT

All manuscripts reporting the results of experimental investigations involving human subjects should include a statement confirming that informed consent was obtained from each subject or subject's guardian, after receiving approval of the experimental protocol by a local human ethics committee, or institutional review board. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed. Research papers not involving human or animal studies should also include a statement that approval/no objection for the study protocol was obtained from the institutional review board, or research ethics committee.