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Research Article

Fatigue in multiple sclerosis

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Abstract. Fatigue is a nonspecific but common symptom in multiple sclerosis (MS). It represents a major cause of disability, affecting the quality of life of MS patients. Most studies on MS fatigue have tried to establish its relationship with disease progression but the results have been contradictory. In view of these previous findings, we conducted a study in order to obtain additional data about fatigue in MS and its clinical correlations. Objective: To evaluate fatigue in MS patients using a specific validated scale and to appreciate its role in the disease's clinical aspects and course, highlighting some specific clinical features in these patients. Material and method: We included in this study 101 patients with MS diagnosis, regardless of disease forms, having the mean age at inclusion of 41.75 years and the female to male ratio of 8.18:1, identified within the records of the Neurology I department of the Emergency County Hospital of Cluj-Napoca. The patients had at least one neurological assessment over the past two years prior to study inclusion (June 2014 - June 2016). "Modified Fatigue Impact Scale" - MFIS was used for fatigue assessment, with a total score of 0 to 84, a higher score indicating greater fatigue. A cut-off score of 38 was chosen to distinguish patients with fatigue from those without fatigue. According to the presence of fatigue (MFIS score ≥ 38), the patients were divided into two groups: the 43 patients with fatigue were included in group A while the 58 patients without fatigue were included in group B. Data related to clinical and imaging features and to disease course were evaluated and compared between the two groups. Results: Fatigue was reported by 43.57% of patients, with a mean MFIS score of 60.97 (standard deviation (SD) 11.81). In group A, MFIS average score was 51.70 (SD 13.57) compared to 18.55 (SD 10.06) in group B. We haven't noticed a difference between the two groups in terms of age at MS onset (29.35 years (SD 9.24) in group A vs 29.9 years (SD 9.87) in group B, p=0.778). Instead, the age at study inclusion was higher in patients with fatigue (45.79 years (SD 11.52) in group A vs 37.71 years (SD 12.97) in group B, p=0.002). As age was higher, the severity of fatigue, as expressed by MFIS score, was greater. The disease duration in group A had the median of 13.17 years (interquartile range (IQR) 9.58 – 19.25), significantly higher than that observed in group B (the median of 6.21 years (IQR 2.67 – 13.83), p < 0.001). The progression to a secondary-progressive (SPMS) form was not different between the group A and B (158.8 vs 141.4 months, p = 0.709) but the SP form was more frequent in patients with fatigue (46.51% vs 8.62%, p < 0.001). An important finding of the study was the association between fatigue and disease severity. The patients in group A had a median EDSS score of 4.00 (IQR 3.0 - 6.0), significantly higher than the median EDSS score of 2.0 (IQR 1.5 - 2.5) observed in group B, p<0.001. Conclusion: Fatigue was an important symptom, commonly found in MS patients, associated to some clinical factors of the disease. We didn't observe an association between fatigue and disease progression. Nevertheless, there was an association with disease severity and its duration.

Key Words: multiple sclerosis; fatigue; disability; disease course.

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Introduction

Multiple sclerosis (MS) is a complex, demyelinating disease of the central nervous system (Gajofatto et al 2013; Boiko et al 2002), considered as the most common cause of progressive neurological disability in young adults, with a major physical, psychological and financial impact (Bamer et al 2008). It represents a chronic, progressive disease with a clinical variable course (Compston et al 2006; Compston et al 2008), in which the interplay between inflammation and neurodegeneration causes the more or less resolutive relapses, and a varying degree of neurological disability (Gajofatto et al 2013).

Fatigue is a nonspecific but common symptom in MS, both in onset and during disease course, some studies reporting its frequency up to 80% (Derache et al 2013; Téllez et al 2006; Bakshi et al 2003). Despite the high-frequency and important clinical impact, the ethiopathogeny of fatigue in MS is not yet fully understood (Boërio et al 2006; Induruwa et al 2012). Several mechanisms have been proposed, but none of them fully explains the fatigue occurrence, underlying its complexity (Iriarte et al 2000). Recent studies highlight the role of axonal damage in the pathogenesis of cerebral atrophy and fatigue (Boërio et al 2006; Induruwa et al 2012). The relationship between depression and fatigue has been also postulated (Pittion-Vouyovitch et al, 2000; Motl et al 2012).

Fatigue represents a major disabling symptom, affecting the quality of life of MS patients (Pittion-Vouyovitch et al 2000). It is defined as a decrease in physical and /or psychological energy, perceived by the patient as interfering with his normal activities (Mills et al 2011).

Being a subjective symptom, its evaluation is difficult and variable interpreted (Flachenecker et al 2002; Chahin et al 2015). There are several rating scales that quantify the severity and impact of fatigue on daily physical, cognitive and psychosocial activities (Krupp et al 1989; Fisk et al 1994; Iriarte et al 1999), mostly being self-assessment questionnaires.

Most studies on fatigue in MS have tried to establish its relationship with disease progression (Induruwa et al 2012; Berger et al 2013). From this point of view, the results have been contradictory concerning the existence of a relationship between fatigue and physical disability (Berger et al 2013). Although several studies have established a positive correlation between the fatigue score and the level of disability expressed by the EDSS score (Flachenecker et al 2002; Niepel et al 2006; Pellicano et al 2010), other studies have found a weak association (Pittion-Vouyovitch et al 2000; Yaldizli et al 2011) or even a lack of association between these factors (Derache et al 2013; Chalah et al 2015). These results are explained by the heterogeneous mechanisms of fatigue and by the different methodology of the studies (Induruwa et al 2012).

In view of these previous findings, we conducted a study in order to obtain additional data about fatigue in MS and its clinical correlations. The objective of the study was to evaluate fatigue in MS patients using a specific validated scale and to appreciate its role in the disease's clinical aspects and course, highlighting some specific clinical features in these patients.

Material and method

This study is an observational and retrospective one, on a cohort of MS patients.

Patients and inclusion criteria

The study population consisted of patients diagnosed with MS, regardless of the disease form (Milo et al 2014; Polman et al 2011), identified within the records of the Neurology I department of the Emergency County Hospital of Cluj-Napoca. The patients had at least one neurological assessment over the past two years prior to study inclusion (June 2014 - June 2016).

The diagnosis and clinical forms of MS have been established according to the international criteria, depending on the period when the diagnosis was confirmed (Poser et al 1983; Polman et al 2005; Polman et al 2011). MS clinical course characteristics were classified according to the existing standardized definitions (Lublin et al 1996).

The following baseline and clinical course parameters were recorded for each patient: sex, date of birth, date and age at onset and at MS diagnosis, clinical picture at onset, initial form of disease (primary progressive or relapsing-remitting), disease duration, relapses history (date and number), first episode of remission (duration, type), level of disability, disease-modifying treatment (date and duration, type of treatment).

The level of disability was assessed using the Expanded Disability Status Scale score (EDSS) (Kurtzke et al 1983). Disease progression was evaluated in terms of period from the onset until the conversion to a secondary-progressive form, and by progression index (PI) of the disease as a measurement of disability accumulation in time (IP = EDSS score/disease duration in years) (Roxburgh et al 2005).

The patients included in the study had performed during the period of maximum 3 months from the last neurological evaluation, a brain +/- cervical-dorsal spinal MRI examination using a 1.5 Tesla MRI and a standard image acquisition protocol for MS. For each patient, imaging data concerning lesion volume (number of T2 lesions), the topography of the lesions, presence of cortical and/or corpus callosum atrophy were recorded.

Data about cognitive and affective status were also obtained for patients who have had a psychological evaluation during a period of maximum three months from the last neurological assessment prior to the study inclusion. The examination was performed by the same examiner, using a uniform battery of tests. To determine cognitive status, Folstein Mini-Mental State Exam (MMSE) scale was used (Folstein et al 1975), with a maximum score of 30. A score greater than 26 was considered as normal (Folstein et al 1975).

Patients were explained the methodology and the objective of the study, emphasizing its observational and non-interventional design. All patients have agreed to participate in the study while preserving the confidentiality of personal data. Also, the study protocol was approved by the Ethics Committee of the "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj Napoca.

Exclusion criteria

- moderate or severe cognitive impairment expressed by a score lower than 20 of a maximum of 30 points on the MMSE; patients diagnosed with dementia were excluded due to the difficulties in understanding and completing the questionnaires used in the study;
- patients with psychiatric disorders under chronic psychiatric treatment;
- patients with an EDSS score ≥ 8.0 or with a severe disability of other causes, which makes impossible questionnaires completion and assessment of fatigue (eg. severe heart or respiratory disease, assets, etc.);

Fatigue assessment

"Modified Fatigue Impact Scale" - MFIS was used for fatigue assessment (Flachenecker et al 2002; Chahin et al 2015). MFIS is a validated, multidimensional scale that analyses the various aspects of fatigue by assessing the impact on physical, cognitive and psychosocial activities. A score of 0 to 4 is assigned to each item, resulting in a total score of 0 to 84, a higher score indicating greater fatigue. The 21 items are classified into three categories: cognitive (score 0-40), physical (score 0-36) and psychosocial fatigue (score 0-8). A cut-off score of 38 was chosen to distinguish patients with fatigue from those without fatigue (Chahin et al 2015), patients being divided into two groups according to the presence of fatigue (MFIS score ≥ 38). The clinical and imaging features were compared between the two groups.

Statistic analysis

Qualitative data were presented as absolute and relative frequencies and mosaic graphic plots respectively. To assess the association between qualitative variables, we used $\chi 2$ test, or Fisher's exact test when the expected frequencies were small. The importance of the link between dichotomous qualitative variables was assessed by the relative risk (RR) with a 95% confidence interval (CI). Normally distributed quantitative data were presented as mean and standard deviation (SD) and graphic diagrams for means with 95% confidence interval. Data that did not follow a normal distribution were presented as median and interquartile range (IQR) and graphically by box whisker plots respectively. Normality evaluation was assessed by Shapiro-Wilk test and by quantile-quantile (Q-Q) plot respectively. Comparisons between independent groups of quantitative data that did not

follow a normal distribution were conducted by Mann Whitney U test, and for data that were normally distributed by t-test for independent samples with equal or unequal variances depending on the Levene test for equality of variances. For all tests a two-tailed p value with a significance level of 0.05 was used. Data processing was performed in the R environment for statistical computing and graphics version 3.2.3.

Results

A total of 136 patients with a diagnosis of MS were identified in the records of the Neurology I department of the County Emergency Hospital of Cluj-Napoca, evaluated in the latest two years, between June 2014 and June 2016. Of these, 35 patients were excluded due to incomplete medical data and investigations. Finally, 101 patients were included in this study. Of these, 90 patients (89.11%) were females (F) and 11 patients (10.89%) males (M), the sex F:M ratio being 8:1.

Only 2 patients (1.98%) had a primary progressive form (SMPP) at MS onset, the other 99 (98.02%) being characterized as having a relapsing-remitting form of MS (RRMS).

Patients were divided in two groups according to the presence of fatigue. Thus, 43 patients (43.57%) with the score MFIS ≥ 38 points that showed fatigue were included in group A. They were fewer by 14.86% when compared to group B consisting of 58 patients (57.43%) without fatigue, with the score MFIS < 38 points.

MFIS average score for the entire patients group was 60.97 (SD 11.81), with values from 2 to 84. In group A, MFIS average score was 51.70 (SD 13.57) compared to 18.55 (SD 6.10) in group B. MFIS scores for each fatigue category (physical, cognitive and psychosocial) observed in the two groups are represented in Table 1.

Table 1. MFIS score by fatigue type in groups A and B

	Patients (n)	Mean years (SD)	P
MFIS score - physical fatigue			<0.001
Group B	58	10.4 (6.42)	
Group A	43	26.95 (6.64)	
MFIS score - cognitive fatigue			<0.001
Group B	58	6.95 (4.41)	
Group A	43	19.51 (7.46)	
MFIS score - psycho- social fatigue			<0.001
Group B	58	1.24 (1.43)	
Group A	43	5.3 (2.2)	

Age

There was no significant association between age at MS onset and fatigue: 29.35 years (SD 9.24) in group A vs 29.9 years (SD 9.87) in group B, p = 0.778. Also, no significant difference was observed among age groups at MS onset (p = 0.265). Among the 15 patients who had less than 20 years at onset, 40% reported fatigue, compared to 47.14% of the 70 patients with onset between 20 - 40 years, and 25% of the 16 patients with onset age more than 40 years.

Instead, we observed a significant association between age at study inclusion and fatigue. The group A had a mean age of 45.79 years at inclusion (SD 11.52), significantly higher (with 8.08 years, p = 0.002) than that observed in group B - 37.71 years (SD 12.97).

Disease duration

We tested the association between disease duration and fatigue and yielded a statistically positive association: 14.29% of those with disease duration less than 5 years had fatigue, compared to 35% of those with a duration between 5 and 10 years and to 60.38% of those with duration more than 10 years (p <0.001). As the disease duration was longer, MFIS score was higher, suggesting a more severe fatigue.

In group A, the disease duration had the median of 13.17 years (IQR 9.58 - 19.25) and values from 2.58 to 44.67 years, significantly higher than that observed in group B - 6.21 years (IQR 2.67 - 13.83) and values from 0.33 to 27.42 years.

Clinical onset

Comparing the two groups (A and B), there was no significant difference in terms of MS onset symptoms. A plurisymptomatic onset was observed in 20 patients (46.51%) in group A and 17 patients (29.31%) in group B. Pyramidal signs were the most frequent onset manifestations in both groups (60.47% vs 43.1%), followed by sensory signs (44.19% vs 39.66%). Only 2 patients (3.45%) presented a clinical picture of encephalopathy and one patient (1.72%) psychiatric disorders, all belonging to group B.

Relapses

We also observed more relapses in group A. The number of relapses in group A had the median of 7 (IQR 6 - 10), significantly higher than that observed in group B - 3 (IQR 2 - 5), p < 0.001. In contrast, the number of relapses during the first 2 years after onset did not vary significantly between the two groups (the median of 2.0 in group A (IQR 1 – 2) vs 2.0 in group B (IQR 1 – 2.75), p = 0.156).

The average duration of first remission had the median of 31 months (IQR 8 - 52), significantly higher than that observed in group B - 11 months (IQR 4 - 23.75), p = 0.005.

Disease progression and the level of disability

No significant difference was observed in the time to secondary-progressive form progression

between the two groups (158.8 months (SD 88.85) in group A vs 141.4 months (SD 69.86) in group B, p = 0.709). However, significantly more patients in group A (46.51%) than in group B (8.62%) have reached the secondary-progressive form of disease (p <0.001).

In order to better assess the accumulation of disability over time, the progression index (PI) of the disease was calculated, but it did not differ between the two groups (p = 0.81). Patients in group A had IP with median of 0.3 (IQR 0.19 - 0.48) compared to those in group B - median of 0.3 (IQR 0.17 - 0.79).

Instead, a positive association between fatigue and EDSS score at diagnosis was observed. EDSS score at diagnosis in group A had a median of 2.0 (IQR 1.5 - 3.0), a value significantly greater than that observed in group B - 1.5 (IQR 1.0 - 2.0), p = 0.001. There was a positive association between fatigue and the actual

EDSS score. Group A had a significantly higher EDSS – median of 4.00 (IQR 3.0 - 6.0) compared to that observed in group B - median of 2.0 (IQR 1.5 - 2.5), $p < 0.001$.

Disease-modifying treatments

The distribution of patients with immunomodulatory treatment, based on the presence of fatigue, is represented in Table 2.

All patients treated with Mitoxantrone had fatigue. Six patients (19.35%) of those with fatigue had previously or currently treatment with Mitoxantrone. There was a positive association between treatment with Mitoxantrone and fatigue ($p = 0.005$). Instead, fatigue was not correlated with a longer duration of immunomodulatory treatment (≥ 5 years), $p = 0.183$. Among the 31 patients with disease-modifying treatment in group A, 20 patients (64.52%) had a treatment for more than 5 years, compared with 20 patients (48.78%) among 41 treated patients in group B. The relative risk was 1.32 (95% CI 0.88 - 1.99).

Table 2. Patients with immunomodulatory drug treatment according to fatigue

Features	Fatigue		p
	Yes n =31	No n=41	
Interferon, no (%)	26 (83.87)	34 (85)	1
Glatiramer Acetate, no (%)	8 (25.81)	7 (17.5)	0.395
Mitoxantrone, no (%)	6 (19.35)	0 (0)	0.005
Natalizumab, no (%)	3 (9.68)	0 (0)	0.079
Other treatment, no (%)	1 (3.23)	2 (5)	1
Treatment duration ≥ 5 years, no (%)	20 (64.52)	20 (48.78)	0.183

Cognitive impairment

Comparing the two groups, we observed that the cognitive impairment, validated by a MMS score < 27, was associated with the presence of fatigue (30.95% in group A vs 5.17% in group B, $p < 0.001$). Some patients experienced depressive elements at psychological evaluation: 17 patients (40.48%) of those with fatigue compared with 13 patients (22.41%) in the other group ($p = 0.052$).

MRI examination

Comparing the groups A and B, a positive association between the presence of lesions in the corpus callosum and fatigue was observed: 36 patients (83.72%) in group A and 36 patients (62.07%) in group B presented corpus callosum lesions. The association between the presence of fatigue and corpus callosum lesions was significant $p = 0.017$. The relative risk was 1.35 (95% CI 1.06 - 1.72).

We also observed a significant difference in terms of fatigue according to the atrophy of the corpus callosum: 27 patients (62.79%) of those with corpus callosum atrophy experienced fatigue compared to 16 patients (27.59%) of those without the corpus callosum atrophy, $p < 0.001$. In terms of cortical atrophy, such association was also significant: 16 patients (66.67%) of those with cortical atrophy experienced fatigue compared to 27 patients (35.53%) of those without cortical atrophy, $p = 0.07$. The relative risk was 1.88 (95% CI 1.241 - 2.84).

Discussions

Fatigue represents a common symptom in MS patients, as reported in 43.57% of patients included in this study. The value is slightly lower than that described in the literature (50-80%), that could be explained by the methodology of the study (Pittion-Vouyovitch et al 2000). In order to better quantify the fatigue, we considered a cut-off limit of 38 points for MFIS score to classify patients as having fatigue, according to some recent studies (Induruwa et al 2012), while the most previous studies did not use this limit. Patients with fatigue had an average MFIS score of 51.70.

In line with other studies (Mills et al 2011), we haven't noted an association between age at onset and fatigue. MFIS scale was applied to fatigue in the last four weeks prior to study inclusion, so that there was no assessment of fatigue as a symptom at MS onset. Instead, we observed a significant association between fatigue and patients age at inclusion (45.79 years vs. 37.71 years). As age was higher, the severity of fatigue, expressed by MFIS score, was greater.

In patients with fatigue, pyramidal signs were the most frequent manifestations at MS onset (60.47%), but we have not observed an association between the presence or severity of fatigue and clinical onset.

Contrary to study of Mills and colab. (Mills et al 2011), fatigue was associated with a longer duration of disease and a higher number of relapses. As the disease duration is longer and lesion activity more intense, degenerative and demyelinating inflammatory changes are more severe, which would result in the occurrence of fatigue, considering its pathophysiology. We observed a positive association between duration of first remission and fatigue. As the duration is longer so MFIS score is higher. However, we found no correlation between the number of relapses in the first two years and fatigue.

We did not observe any significant association between fatigue and disease progression. The time to reach the secondary-progressive form did not vary significantly between the two groups. In contrast, secondary-progressive form was significantly more frequent in the group of patients with fatigue. The index of disease progression did not differ significantly between the two groups although there was an increasing trend in the group of patients without fatigue, suggesting a faster progression of the disease.

An important finding of the study was the association between fatigue and disease severity. In accordance with the results of previous studies (Pittion-Vouyovitch et al 2000; Bakshi et al 2000) we observed a positive association between fatigue severity and the degree of disability. As MFIS score was higher the degree of disability expressed by the EDSS score was higher, both at diagnosis and at study inclusion. But these results were not confirmed by other studies (Pittion-Vouyovitch et al 2000; Bakshi et al 2000), which failed to find a correlation between fatigue and the degree of disability. This discrepancy could be explained both by the different methodology of the studies, some of them including small populations of patients and by the difficulty to diagnose fatigue in MS and the use of different measurement instruments.

In terms of disease-modifying therapy, Interferon beta and Glatiramer Acetate were the most used in the group of patients with fatigue (83.87% and 25.81%). A positive association between treatment with Mitoxantrone and fatigue was observed.

All patients treated with Mitoxantrone showed fatigue, but the number of patients was small (19.35%). This association is explained by the link between fatigue and the disease severity discussed above, knowing that Mitoxantrone is indicated in more severe and aggressive forms of disease. Instead, any association with Interferon, Glatiramer Acetate treatment or duration of treatment (> 5 years) was observed. Despite the fact that immunomodulatory treatment reduces inflammatory activity, fatigue remains an important symptom of the disease (Putzki et al 2009). The impact of immunomodulatory therapy on fatigue remains unclear and requires further randomized, prospective trials (Putzki et al 2009).

Another important result of the study was the association between the mild cognitive impairment and fatigue, an MMSE score <27 being more frequently observed in the group of patients with fatigue. It is known that cognitive impairment is common in patients with MS. At the same time, fatigue can alter cognitive test results but a clear relationship between these two parameters has not been established.

The study of depression in both groups showed an association between this one and fatigue, of borderline significance, depression being more frequent in the group of patients with fatigue (40.48% vs 22.41%). The literature shows that depression is a common symptom in MS patients, reporting a prevalence of 24-40% (Pittion-Vouyovitch et al 2000; Induruwa et al 2012). Fatigue is common both in patients with depression and in MS patients. Although a correlation between fatigue and depression has been suggested, it is assumed to be complex and multifactorial (Pittion-Vouyovitch et al 2000; Induruwa et al 2012). Kroencke et al (Kroencke et al 2000) have shown that depression and disability are important predictors of fatigue in MS. However, treatment of depression does not lead to remission fatigue.

Regarding the imaging findings, a significant association was observed between fatigue and the presence of corpus callosum lesions, corpus callosum atrophy and cortical atrophy changes commonly seen during the course of MS. This association suggests the role of diffuse axonal loss and neurodegeneration in the pathogenesis of fatigue.

Conclusion

Fatigue was an important symptom, commonly found in MS patients, associated to some clinical factors of the disease. We didn't observe an association between fatigue and disease progression. Nevertheless, there was an association with disease severity and its duration.

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