

Conceptual definition of fatigue and selected specific time characteristics of fatigue in patients with multiple sclerosis

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Key words: fatigue, patient, multiple sclerosis.

Abstract

Introduction: Patients with multiple sclerosis (MS) experience fatigue as a subjective symptom with inter-individual variability. Fatigue is present at any time during the course of the disease, with varying durations over a period of time.

Aim of the research: To determine the conceptual definition of fatigue in adult patients with MS and to describe fatigue over a given time period.

Material and methods: 147 patients with MS (Group A) and 158 controls (Group B) participated in the quantitative prospective cross-sectional study. The questionnaire contained items focused on conceptual definition of fatigue, its duration during the day and its frequency during the week. The χ^2 test of independence and the Student's *t*-test for two independent samples were used for statistical analysis.

Results: Group A significantly more often than Group B perceived fatigue as muscle weakness, physical tiredness, whole body exhaustion, lack or absence of physical and mental strength, greater effort when performing activities, tired/heavy legs, increased tiredness, memory difficulties, problems with concentration, impatience, despondency, and apathy. Group A reported significantly longer duration of fatigue (4.82 hours) than Group B (2.49 hours) in 24 hours. The incidence of fatigue in 7 days was significantly more frequent in Group A (5.26 days) than in Group B (3.01 days).

Conclusions: Understanding the conceptual definition and duration of fatigue leads to an effective management of the disease symptoms.

Introduction

Multiple sclerosis (MS) is a neurological progressive autoimmune disease of the central nervous system characterized by a chronic inflammatory process, the formation of demyelinating lesions, and presence of a wide spectrum of symptoms leading to a variety of neurological impairments, due to the nature of the lesions. Currently, MS affects 2.8 million people worldwide. In North America and Europe, it is the main cause of chronic nontraumatic neurological diseases in young adults [1]. MS symptoms may have a variable influence on the quality of life of each patient [2]. Fatigue is the most prevalent issue for MS patients. It affects 75–95% of them. Fatigue can occur at all stages of MS and is one of the most often reported and most disabling symptom [3–5]. It is associated with various health problems, depression, anxiety, motor function, and sleep patterns [3]. Fatigue is the most commonly reported impairment in everyday life activities [2]. In patients with MS, fatigue is considered a multidimensional symptom, manifesting itself in distinct dimensions such as physical (motor), cognitive (mental), and psychosocial fatigue. Due to the inter-individual variability of manifestations and the subjectivity of the feeling of fatigue [6, 7], there are many definitions of

fatigue [8]. The multidimensionality of fatigue in MS patients is still not sufficiently understood [9]. Fluctuations of fatigue during the day are typical for this group of patients compared to a healthy population; it occurs on a daily basis; worsens as the day progresses; comes on more easily and suddenly; and it is more severe than normal fatigue [4, 10].

Aim of the research

First, to determine the conceptual definition of fatigue in patients with multiple sclerosis, and second, to determine and describe fatigue in terms of specific time characteristics.

Material and methods

The sample consisted of 305 adult respondents, including 147 patients with MS, who met predefined classification criteria: age ≥ 18 years, MS (G35) diagnosed by a specialty physician, duration of MS of at least 1 year, no attack/relapse in the last 4 weeks (30 days), without depression (as determined by a specialty physician)/depression in a personal history with a minimum duration of treatment of 3 months, additional organic causes in personal history (e.g. car-

diovascular, blood, endocrine diseases) with a minimum duration of treatment of 3 months, regardless of the state of incapacity according to the Expanded Disability Status Scale (EDSS), willingness to fill out a questionnaire, and recommendation to participate in the study. The study participants who did not meet at least one of the above-mentioned criteria were excluded from the sample. We also included controls in our study to distinguish from the group of subjects with MS, which is consistent with several studies [11, 12]. The control group consisted of 158 participants who signed informed consent.

Study design: quantitative prospective cross-sectional study.

Empirical data collection: A quantitative method was used for data collection – a questionnaire divided into several parts. The study presents part of the items designed for fatigue management, such as the conceptual definition of fatigue, its frequency and duration (in hours) during 24 hours and during 7 days (a week). We created the items in the questionnaire based on the personal experience of MS patients with fatigue, several international studies [13–16] as well as the definition of fatigue in the nursing diagnosis (00093) [17]. Gender, age, working status, duration of MS, associated diseases in personal history were obtained from the demographic data. Type of MS and EDSS were checked in the patient's medical records with the consent of the attending physician.

Collection of the empirical data took place in printed form at the Neurological Clinic of University Hospital in Martin (UHM) and JFM CU from 08/2020 to 02/2021.

Statistical analysis and evaluation of empirical data

Empirical data were evaluated in the statistical program SPSS, version 22.0 and Jamovi 2.3.2 program. Descriptive statistics included absolute (N) and relative (%) frequency, arithmetic mean (M), standard deviation (SD), minimal (min.) and maximal (max.) values. The χ^2 test of independence and the Student's *t*-test for two independent samples were used. If the analyzed differences between the two groups were categorical, the χ^2 test of independence was used. We reported its value (χ^2) with degrees of freedom (df) and statistical significance (*p*). Student's *t*-test was used when two groups were compared on an interval variable. We reported its value (*t*) with degrees of freedom (df) and statistical significance (*p*). In addition to statistical significance with a given significance level of $\alpha = 0.05$, we also calculated practical (substantive) significance through effect size indices (Effect Size, ES). In the case of the χ^2 , we used the coefficient phi (ϕ), and for the Student's *t*-test, Cohen's *d* was calculated [18–20]. Empirical data were tested at a significance level of 5% ($p < 0.05$).

Results

The results in Table 1 present selected demographic characteristics. In Group A with an average age of 41 years, the majority were women (70.7%). Most of the participants were on disability pension at that time (43.5%). The average duration of MS was 8.26 years. RR-MS type was the most common (88.4%). The average EDSS score was 3.43 points and most patients had a neurological disability assessed according to EDSS as minimal (61.2%). 91.2% of subjects lived in a joint household. Associated diseases were reported by 73.5%; the most of which were cardiovascular diseases (9.5%). In Group B with an average age of 44 years, the majority were women (70.3%) and 70.3% were employed. 93% of controls lived in a joint household. Associated diseases were reported by 59.5%, most of which were cardiovascular diseases (20.3%).

Table 2 shows the results of the conceptual definition of fatigue in both groups. Group A most often defined fatigue as a heavy/tired leg (63.9%) and muscle weakness (63.3%) and Group B as sleepiness (69%). Group A significantly more often than Group B perceives fatigue as muscle weakness ($p = 0.001$), physical tiredness ($p = 0.047$), whole body exhaustion ($p = 0.001$), lack or absence of any physical and mental strength ($p = 0.001$), need for greater effort when performing activities ($p = 0.001$), slowness ($p = 0.001$), tired/heavy legs ($p = 0.001$), increased tiredness ($p = 0.001$), memory difficulties ($p = 0.001$), problem with concentration ($p = 0.042$), impatience ($p = 0.001$), despondency ($p = 0.041$), apathy ($p = 0.035$). The substantive significance of the phi coefficient was from low to medium ($\phi = <0.114; 0.458>$).

According to the results in Table 3, fatigue over a period of 24 hours lasted an average of 4.82 hours in Group A and 2.49 hours in Group B. Group A reported significantly more hours of fatigue lasting during the day than Group B ($t(303) = 6.464, p < 0.001$). The substantive significance was high (Cohen's $d = 0.704$). The frequency of fatigue during the week was on average higher in Group A ($M = 5.26$ days) than in Group B ($M = 3.01$ days). Group A reported a significantly higher frequency of fatigue during the week than Group B ($t(303) = 9.981, p < 0.001$). The substantive significance was high (Cohen's $d = 0.791$). In a period of 24 hours, fatigue occurred in Groups A and B most often in the lunch and afternoon hours (57.2% vs. 41.8%). In Group A (19%) and in Group B (1.8%), subjects reported the occurrence and duration of fatigue throughout the day (approx. 18 hours).

Discussion

The first aim of our study was to determine the conceptual definition of fatigue in patients with MS. Perception of fatigue is a physiological response to prolonged activity or short and intense activity in

Table 1. Demographic characteristics of the sample ($N = 305$)

Demographic variables	Group A ($N = 147$) N (%)	Group B ($N = 158$) N (%)
Sex		
Female	104 (70.7)	111 (70.3)
Male	43 (29.3)	47 (29.7)
Age [years] (mean $\pm$ SD) (min., max.)	41.05 $\pm$ 9.83 (18, 63)	44 $\pm$ 15.49 (18, 73)
Employed/working status		
Employed/working	56 (38.1)	111 (70.3)
Unable to work	20 (13.6)	2 (1.3)
Invalidity/disability pension	64 (43.5)	1 (0.6)
Old-age pension	2 (1.3)	20 (12.7)
Student	5 (3.4)	24 (15.2)
Types of MS		
RR-MS (relapsing remitting MS)	130 (88.4)	–
SP-MS (secondary progressive MS)	10 (6.8)	–
PP-MS (primary progressive MS)	7 (4.8)	–
Length of MS [years] (mean $\pm$ SD) (min., max.)	8.26 $\pm$ 5.83 (1, 30)	–
EDSS [points] (mean $\pm$ SD) (min., max.)	3.43 $\pm$ 1.73 (1, 7.5)	–
Neurological disability MS according to EDSS		
Minimal (≤ 4.0)	90 (61.2)	–
Mild (4.5 – 6.5)	54 (36.7)	–
Severe (≥ 7.0)	3 (2.0)	–
Housing		
Alone	13 (8.8)	11 (7.0)
Living with someone	134 (91.2)	147 (93.0)
Associated diseases in personal history		
Yes	108 (73.5)	94 (59.5)
No	39 (26.5)	64 (40.5)
The most common diseases in personal history		
Cardiovascular diseases	14 (9.5)	32 (20.3)
Endocrine diseases (thyroid disorder)	10 (6.8)	12 (7.6)
Allergies	–	11 (7.0)
Diseases of uropoietic system/urinary tract	6 (4.1)	–
Mental illnesses/disorders	6 (4.1)	–

A – Group of patients with MS, B – Control group, N – absolute frequency, % – relative frequency, M – arithmetic mean, SD – standard deviation, min. – minimal value, max. – maximal value.

both MS patients and healthy individuals [21]. Fatigue is most often defined in MS patients as a feeling of lack of energy, weakness and aversion to exertion [3]. According to the results of our study, patients with MS defined fatigue as physical, mental and psychosocial fatigue. Most of them stated the presence of several types of fatigue at the same time in the conceptual

definition. Concerning physical fatigue, patients with MS mentioned heavy/tired legs, muscle weakness, sleepiness, body exhaustion, whole body exhaustion, and increased tiredness. Mental fatigue was most often expressed as problems with concentration, and psychosocial fatigue as inner restlessness and irritability. Controls reported sleepiness and physical exhaustion

Table 2. Content definition of the term fatigue in Group A and Group B

Content definition of the term fatigue	Group A (N = 147) N (%)	Group B (N = 158) N (%)	χ^2	df	P-value	ϕ
Muscle weakness	93 (63.3)	29 (18.4)	64	1	0.001	0.458
Physical tiredness	80 (54.4)	68 (43)	3.95	1	0.047	0.114
Whole body exhaustion	78 (53.1)	39 (24.7)	25.90	1	0.001	0.292
Lack or absence of physical and mental strength	39 (26.5)	14 (8.9)	16.60	1	0.001	0.233
Greater effort when performing activities	63 (42.9)	33 (20.9)	17	1	0.001	0.236
Slowness, “everything takes me a long time”	70 (47.6)	35 (22.2)	21.90	1	0.001	0.268
Tired/heavy legs	94 (63.9)	47 (29.7)	35.80	1	0.001	0.343
Increased tiredness	77 (52.4)	30 (19.0)	37.30	1	0.001	0.350
Malaise	45 (30.6)	42 (26.6)	0.61	1	0.436	0.045
Drowsiness	86 (58.5)	109 (69.0)	3.63	1	0.057	0.109
Memory difficulties	42 (28.6)	11 (7.0)	24.80	1	0.001	0.285
Problems with thinking	41 (27.9)	39 (24.7)	0.45	1	0.501	0.039
Problems with concentration	55 (37.4)	42 (26.6)	4.12	1	0.042	0.116
Impatience	37 (25.2)	16 (10.1)	12	1	0.001	0.198
Despondency	50 (34.0)	37 (23.4)	4.19	1	0.041	0.117
Inner restlessness, irritability	66 (44.9)	55 (34.8)	3.24	1	0.072	0.103
Lack of motivation to act, “unwillingness to do anything”	54 (36.7)	47 (29.7)	1.68	1	0.195	0.074
Apathy	32 (21.8)	20 (12.7)	4.47	1	0.035	0.121

A – Group of patients with MS, B – Control group, N – absolute frequency, % – relative frequency, χ^2 – Chi square, df – degrees of freedom, p – statistical significance, $p < 0.05$, ϕ – substantive significance of the phi coefficient.

Table 3. Frequency of fatigue in a certain period of time in Group A and Group B

The duration of fatigue over a certain period of time	Group A (N = 147) (mean $\pm$ SD)	Group B (N = 158) (mean $\pm$ SD)	t	df	P-value	d
Number of hours/24 hours	4.82 $\pm$ 4.03	2.49 $\pm$ 1.77	6.464	303	< 0.001	0.704
Number of days/7 days	5.26 $\pm$ 2.02	3.01 $\pm$ 1.91	9.981	303	< 0.001	0.791
The most frequent time interval of fatigue/24 hours	Group A (N = 147) N (%)	Group B (N = 158) N (%)				
Afternoon (noon – 5:00 p.m.)	84 (57.2)	66 (41.8)				
Evening (5:00 p.m. – 11:00 p.m.)	25 (17.0)	65 (41.1)				
The whole day (6:00 a.m. – 11:00 p.m.)	28 (19.0)	3 (1.8)				

A – Group of patients with MS, B – Control group, N – absolute frequency, % – relative frequency, M – arithmetic mean, SD – standard deviation, t – Student's t-test value, df – degrees of freedom, p – statistical significance, $p < 0.05$, Cohen's d – index of objective significance.

as the most common characteristics of physical fatigue. Most controls described mental fatigue as problems with concentration, and psychosocial fatigue as restlessness and irritability. In this context, it is necessary to stress that the perception of fatigue in patients with MS is different from the perception of the healthy population, and the subjective perception of fatigue does not correlate with objective physical signs [9].

Physical and mental fatigue are bothersome for patients with MS and affect their normal daily life [22]. According to patients with MS, they have great difficulty expressing fatigue with words and/or concepts; but it is certainly different from the fatigue they perceive after work or sports activity [23]. The claim of the authors [15] that fatigue causes a very subjective response as each person perceives fatigue in

a different way, was also confirmed by the patients in our study (e.g. “I can’t describe it”, “it’s hard for me to express it verbally”). In our study, the conceptual definition of fatigue, expressed in descriptors such as increased fatigue, weakness, general clumsiness and movement coordination problems in patients, is the result of the pyramidal tract lesions in the pathophysiology of MS. Increased fatigue and motor weakness make it difficult to endure physical exertion for a certain period of time [24]. The lack of physical and mental strength is also related to the lack or absence of motivation for activities requiring physical effort [25]. The fluctuations of the mentioned MS symptom may be behind the verbalization of reluctance to do anything or even apathy (psychosocial fatigue), which is related to the patient’s inability to finish the activity started or to start doing it at all [26]. Muscle weakness is related to physical fatigue during exercise, workout, which leads to muscle exhaustion. Thus, patients report a loss of strength in the extremities/limbs, which leads to deterioration of walking and speech, fine motor skills and coordination of movements [16, 27]. The feeling of heavy/tired legs in patients with MS is related to a rapid loss of energy in the muscles of not only the lower limbs, and also to a disturbance in the conduction of nerve impulses through the motor pathways in the central nervous system, which results in impaired walking and coordination of movements and increases the risk of tripping and falling [9, 28, 29]. Unlike fatigue in healthy people, MS-related fatigue is more likely to interfere with role performance and physical functioning [10].

Mental fatigue or its concept has not yet been sufficiently studied in patients with MS [22], but it worsens cognitive functions (e.g. memory, attention, concentration, information processing, reduced reaction time response, alertness during the day, difficulty in thinking, word finding). Cognitive fatigue is not related to physical disability at the onset of the disease, and patients may complain of its presence even before the diagnosis of MS [30]. The above-mentioned problems also lead to a feeling of psychosocial fatigue [22], which is expressed in the form of anxiety, anger, sadness, and helplessness over the disease, feelings of failure and fear, and disturbed emotional stability [13].

The second aim was to determine and describe fatigue in terms of specific time characteristics. According to the results of our study, patients with MS (Group A) reported a higher frequency of fatigue occurrence over a certain period of time than controls in Group B, which is in accordance with the reported characteristics of fatigue for this group of patients compared to the healthy population [4, 10]. The negative effect of fatigue is that it affects the patient’s ability to participate in physical activities [13]. They are able to carry out physical activities independently and without problems in the morning and afternoon. The problem may arise, however, in the afternoon,

which means that they can’t do any physical activity at all or they need help from others. This is a typical example of diurnal fluctuation of physical fatigue [26]. The occurrence of fatigue at least 2 times a week was reported by up to 76% of patients with MS [13]. Fatigue therefore persists throughout the week, which is characteristic of chronic MS disease, thus, we may talk about chronic fatigue in this group of patients [31]. Patients report that they are tired most days [16]. In this context, it should be noted that fatigue may be transient, prolonged, chronic, or intermittent [32]. Similar to another study [33], in our study, the duration of fatigue in patients with MS was significantly longer in 24 hours, and most of them reported its occurrence during lunch and in the afternoon. In the study of Mills and Young, patients reported the most frequent occurrence of fatigue in the afternoon and evening [16]. The higher incidence of fatigue in patients with MS may also be related to the fact that cognitive fatigue worsens during the day, mainly in the afternoon compared to the morning [34].

Limitations: The research study was carried out in one regional medical facility and the sample size does not allow for generalization of the study results.

Conclusions

The results of the study showed a wide variability in the conceptual definition of fatigue, which points to the multidimensionality of the given symptom in MS. Based on subjective experience, patients reported the presence of physical, cognitive and psychosocial fatigue at the same time. The duration and frequency of fatigue in a certain period of time in patients with MS is different in the control group. Defining the term fatigue in a given group of patients based on their subjective experience, duration and frequency of its occurrence over a certain period of time are the basis for a better understanding of the symptoms of MS and effective management of fatigue.

In the context of effective management of fatigue in patients with MS, the results of the study can also be a useful starting point for further research into factors related to the origin and minimization of fatigue.

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Ethical approval

We asked the head of the Clinic of Neurology of the UHM for permission to access the archives of patients’ medical records and collect data (written consent). The study was approved by the Ethics

Commission of the UHM (No. 85/2020). The protocol for the research project conforms to the provisions of the Declaration of Helsinki of 1989.

Conflict of interest

The author declares no conflict of interest.

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