A prospective study of patterns of fatigue in Multiple Sclerosis

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Running title: Patterns of fatigue in multiple sclerosis

The statistical analysis was conducted by A. Lerdal, RN, PhD and AA. Dahl, MD, PhD.

Keywords: Multiple sclerosis, Fatigue, Quality of Life, Depression, and Cohort studies.

Disclosure: The authors report no conflicts of interest.

Acknowledgement: Buskerud University College, Drammen, Norway and Odd Fellow Research Fund, Oslo, Norway have funded this research.

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Abstract

We sought to identify clinical characteristics and socio-demographic variables associated with longitudinal patterns of fatigue in MS patients.

A questionnaire including the Fatigue Severity Scale (FSS) was mailed to a community sample of 502 MS patients three times one year apart. Three patterns of fatigue were defined: persistent fatigue (PF) (mean FSS-score ≥5 at all time-points), sporadic fatigue (SF) (mean FSS-score ≥5 at one or two time-points) and no fatigue (mean FSS-score <5 at all time-points).

Among the 267 (53%) patients who responded at all time points, 101 (38%, 95%CI 32-44) had persistent, 98 (37%, 95CI 31-43) sporadic and 68 (25%, 95%CI 20-31) no fatigue. Persistent and sporadic fatigue were more common in patients with, increased neurological impairment ($p<0.001$), primary progressive MS ($p=0.01$), insomnia ($p<0.001$), heat sensitivity ($p<0.001$), sudden-onset fatigue ($p<0.001$) or mood disturbance ($p<0.001$) compared to patients without fatigue. Multivariable analysis showed that depression (PF $p=0.02$, SF $p<0.001$), heat sensitivity (PF $p=0.04$, SF $p=0.02$), and physical impairment (PF $p=0.004$, SF $p=0.01$) were associated with both sporadic and persistent fatigue.

75% of the patients had persistent or sporadic fatigue over a two years observation period. Multivariable analyses confirmed a significant association between levels of depression, physical impairment and persistent fatigue.

Introduction

Fatigue can be defined as a sense of exhaustion, lack of perceived energy and tiredness [1,2], distinct from sadness or weakness [3]. Fatigue is one of the most common symptoms in multiple sclerosis (MS)[4] and has been characterized as 'severe' in 64-83% of patients with MS [5,6]. Features significantly associated with severe fatigue include physical impairment, elevated levels of psychological distress and sleep problems [5,7-9]. While fatigue has been characterized in several cross-sectional studies of MS patients, little is known regarding the longitudinal course of fatigue.

The aim of this longitudinal prospective community-based study was to identify longitudinal patterns of fatigue in MS patients, and to explore the associations of socio-demographic and clinical variables to these patterns.

Methods

Patient sampling

Data was collected at three time points in May/June, one year apart with start in 2000. Based on the Oslo City MS Registry [10] 502 patients with definite MS according to Poser criteria [11], were invited to participate in the study. At baseline, 368 (73%) responded, and 267 (53%) filled in all the questionnaires at all time-points.

Data regarding age, sex, disease course, time since onset and diagnosis were retrieved from the MS registry. Disease course was defined as either relapsing remitting (RR) including secondary progressive (SP), or primary progressive (PP) [11].

Measurements

Data on socio-demographic background, fatigue, anxiety and depression, level of physical functioning (PF), insomnia and ADL were collected trough the mailed-out questionnaire. The patients stated their highest level of formal education.

Fatigue was self-rated by the *Fatigue Severity Scale (FSS)* [12] which consists of 9 statements regarding fatigue experiences. Patients were asked to whether they disagreed (1) or agreed (7) using a Likert scale ranging from 1 – 7. Higher scores indicate higher levels of fatigue. Patients with a mean FSS score ≥5 were defined as having severe fatigue. The FSS is the most commonly used instrument to measure fatigue among MS patients and has shown high validity and reliability [12-14]. Internal consistency of the FSS at t_1 assessed by Cronbach's α was 0.90.

At all three time-points a FSS mean score for each patient was calculated. Based on the FSS sum scores at all three time points, the sample was separated into three groups: 'never fatigue' = FSS sum scores <5 on all time points; 'sporadic fatigue' = severe fatigue at one or two time points; and 'persistent fatigue' = severe fatigue at all three time points.

Anxiety and depression were self-rated using the subscales of *Hopkins Symptom Checklist (HSCL)* named accordingly with 25 items altogether [15]. Cronbach's α was 0.80 for the anxiety items and 0.90 for the depression items in our sample.

The level of PF was self-rated using the *Short Form-36 (SF-36*) [16]. The SF-36 is a questionnaire that measures physical and mental issues related to health-related quality of life (QoL). Higher scores correspond to better perceived QoL. The SF-36 has demonstrated satisfactory reliability and validity [17,18]. Cronbach's alpha was 0.95 for the PF items in the present study. The SF-36 PF has been demonstrated to have a linear relationship and a high correlation (r = –0.86) [19] with neurological impairment among MS patients' as assessed by Kurtzke's expanded disability scale (EDSS) [20].

An *insomnia index* was made from the means scores of three items developed for this study based on the ICD-10 diagnosis of F51.0 'non-organic insomnia' [21] i.e. the patients were asked if they had experienced difficulties getting to sleep, sleeping during night and being awake during the day, or of waking up too early in the morning during the last 2-weeks. The response alternatives were 'not at all' (1), 'very little' (2), 'quite much' (3) or 'often' (4). The responses had an internal consistency of Cronbach's α was 0.82. In addition, one question examined if the patients had experienced any sleep problems related to nocturia (not included in the insomnia index).

Data on heat sensitivity were collected by an item asking to what degree warm weather or high indoor temperature influenced the patients' experience of fatigue. Response alternatives were on a Likert scale ranging from 'not at all' (1) to 'to a high degree' (6). Several items of the questionnaire investigated whether their fatigue experience had influenced their performance of different *ADL functions* (i.e. doing housework, visiting friends, reading a book, having visitors, moving around, getting dressed, performing the daily care, doing the cooking, shopping, or practicing hobbies). The patients were also asked if their fatigue had a sudden onset. Those who responded 'not at all' or 'to some degree' were defined as without difficulties performing ADL while those who responded 'very difficult' or 'impossible' were defined as having problems with ADL. The patients were also asked whether or not they were taking medication including disease-modifying therapies.

Statistical analysis

The data were analysed using SPSS for Windows Version 14.0 software (SPSS Inc., IL, USA). *T*-tests and oneway ANOVA with post hoc Bonferroni corrections were used to analyze continuous variables. Data on ordinal and categorical level was analyzed using chi-square. Pearson's correlation was used for correlation analyses. Effect sizes (ES)

were calculated on the dimensional differences between the groups according to Cohen's coefficient d. d values ≥0.40 were considered as clinically significant [22]. Logistic regression was used to test for significant predictors of sporadic and permanent fatigue. The strength of association was expressed as odds ratios (ORs) with 95% confidence intervals (95%CI). The group with 'never fatigue' was used as a reference. Cronbach's alpha [23] was used to assess the internal consistency of the scales. The level of significance was set at $p<0.05$, and all tests were two-tailed.

Ethics

The Regional Medical Research Ethics Committee of Health East of Norway and the Norwegian Data Inspectorate approved the study. Informed written consent was obtained from all patients.

Results

Attrition analysis

Patients who participated at all three time points had a lower mean age (M=49.0 years, SD=10.8) than those who did not (M=51.7 years, SD=13.5, p=0.01). The proportion of women (74.9%, p=0.02) was higher among patients at all time points. Mean time since onset was lower among responding patients (M=16.5 years, SD= 9.9) than among the non-respondents (M=19.2 years, SD=11.9, p=0.01). The effect size of these findings were all <0.25 and not considered clinically significant. Patients showed no differences with regards to mean time since diagnosis (11.1 years, SD= 8.2) or the proportion of RR/SP MS disease course (82%, n=220) compared to the non-respondents.

Demographic findings

There were no differences between the three fatigue groups in relation to mean age or the proportion of those with high level of education, living in a paired relationship or the different social classes at baseline (Table 1).

Table 1 about here

Clinical findings at baseline

The persistent fatigue group had a significant higher proportion of patients who were not working, who had a PP disease, who were using more aids and medication than among those with never fatigue. Scores on anxiety, depression and PF showed significantly differences between the never, sporadic and persistent fatigue groups. Patients with persistent fatigue had the highest scores on anxiety and depression, and the lowest scores on PF. Insomnia and heat sensitivity were scored higher in the sporadic and persistent fatigue groups versus the never fatigue group (Table 2).

Table 2 about here.

On most ADL functions a higher proportion of patients with persistent fatigue showed problems compared to those with sporadic and never fatigue. Patients with high scores on depression also frequently reported insomnia (r=0.52) and higher anxiety scores (r=0.65). Due to the high correlation between depression and anxiety, only depression was included in the regression analysis.

In univariable analyses not working, using medication, low PF, high depression, insomnia, suddenly fatigue and heat sensitivity scores were all significantly associated with caseness of sporadic and persistent fatigue with never fatigue as reference (Table 3).

Table 3 about here

The multivariable analysis showed that low PF, high depression, and heat sensitivity scores were significant predictors of both sporadic and persistent fatigue compared to those with never fatigue.

Insomnia, controlling for socio-demographic and clinical variables including heat sensitivity, did not show any independent relationship with sporadic or persistent fatigue.

Discussion

This is the first study to our knowledge which has studied patterns of MS associated fatigue longitudinally, identified predictors of sporadic and persistent fatigue, and examined the impact of these patterns of fatigue on the patients' performance of ADL. The sporadic and persistent patterns of fatigue was equally prevalent in our sample (38 versus 37%), and were significantly more common than no fatigue. Having persistent fatigue was significantly related to less capacity to work and increased neurological impairment. These negative effects were stronger for patients with persistent fatigue than those who have sporadic fatigue. Persistent fatigue also had a negative impact on the patients' performance of ADL especially doing housework, visiting friends, moving around and doing shopping. Several studies have reported that fatigue is related to reduced QoL [9,24]. After controlling for possible confounders, neurological impairment, depression and heat sensitivity significantly predicted both sporadic and persistent fatigue compared to those with never fatigue.

As reported in several cross sectional studies, depression and physical impairment have shown a strong independent relationship with fatigue [7,25]. These relationships have also been reported in studies measuring fatigue at two time points one year apart [9,26]. The use of fatigue caseness as a dependent variable in the statistical analyses indicates a causal relationship. However, theoretically fatigue might also contribute to depression. Furthermore, there may be different types of MS-fatigue e.g. a depression related fatigue different from and a heat related fatigue.

The relationship between disease course and fatigue has been shown to be mediated by lower PF among those with a progressive disease [9]. The previously reported relation between insomnia and fatigue [5] has to some degree been confounded by depression [7]. The relationship between insomnia and fatigue in MS has also shown to be related to physical symptoms such as nocturia, bladder incontinence, pain and leg spasms [5,27].

The relatively strong relationship between having a heat sensitivity and sporadic or persistent fatigue is described in the literature. Except for intervention studies on the use of cooling-suits or cooling therapy [28-31] few empirical studies have explored the mechanisms of heat sensitivity. However, core temperature during simulated work activity has shown to be higher among patients with MS than healthy controls [32].

Since no clinically significant differences were observed between patients who filled in the FSS at all time points, and those who did not, with some reservation we can generalize the fatigue patterns and their associations to all MS patients.

Clinical implications

Over a two years observation period 60–70% of the patients have a pattern of either persistent or sporadic fatigue which has an impact on ADL. Our findings imply that severe fatigue in MS patients may have a less static pattern than formerly believed i.e. the intensity of fatigue was varying among half of those which experience fatigue. However, since sporadic and persistent severe fatigue has strong impact on ADL that patients need to perform in their everyday life, health care workers need to assess their fatigue and help them to managing it.

Table 1. Demographic and clinical characteristics of the sample at baseline.

	Never fatigue (n = 68)	**Sporadic fatigue** (n = 101)	**Persistent fatigue** (n = 98)	**P**
Demographic variables				
Age, mean (SD)	46.4 (9.5)	49.5 (11.6)	49.4 (10.8)	0.14
	N (%)	*N (%)*	*N (%)*	
Males	18 (26)	25 (25)	25 (25)	0.97
Females	50 (74)	76 (75)	73 (75)	
Education				0.79
< 13 years	36 (53)	57 (57)	57 (58)	
≥ 13 years	32 (47)	43 (43)	41 (42)	
Being in paired relationship	33 (48)	56 (55)	52 (53)	0.68
Work status				<0.001
Working	50 (74)	51 (51)	4 (35)	
Not working	18 (26)	50 (49)	64 (65)	
Social class				0.40
Class I	28 (41)	49 (48)	40 (41)	
Class II	27 (40)	34 (34)	31 (32)	
Class III	13 (19)	18 (18)	27 (27)	
Clinical variables				
Disease course				0.01
RR/SP-MS	63 (93)	84 (84)	71 (73)	
PP-MS	5 (7)	16 (16)	26 (27)	
Years since onset	15.6 (9.3)	16.4 (10.6)	17.9 (9.4)	0.67
Use of aids				
Crutches	1 (2)	7 (8)	13 (14)	0.019
”Walk-chair”	5 (7)	20 (20)	17 (18)	0.65
Wheel-chair	7 (10)	25 (26)	23 (25)	0.037
Use of medication				
Yes	40 (59)	82 (81)	75 (77)	0.004
Co-morbidity	12 (19)	24 (26)	23 (25)	0.56

Table 2. Clinical characteristics at baseline.

	Never fatigue (n = 68) ***Mean (SD)***	**Sporadic fatigue** (n = 101) ***Mean (SD)***	**Persistent fatigue** (n = 98) ***Mean (SD)***	**P**
SF-36 – PF	77.1 (27.5)	50.0 (32.4)	38.9 (26.6)	<0.001, N vs S vs P
Insomnia (1–4)	1.4 (0.5)	1.8 (0.7)	1.9 (0.8)	<0.001, N vs S, P
Heat sensitivity (1–6)	2.4 (1.4)	3.6 (1.7)	4.0 (1.7)	<0.001, N vs S, P
Anxiety (1-4)	1.2 (0.2)	1.4 (0.4)	1.6 (0.5)	<0.001, N vs S vs P
Depression (1-4)	1.3 (0.3)	1.6 (0.5)	2.0 (0.6)	<0.001, N vs S vs P
	N (%)	***N (%)***	***N (%)***	
Suddenly fatigue	19 (28)	44 (44)	59 (60)	<0.001
Sleep problems cased by nocturia	9 (13)	12 (12)	23 (24)	0.078
Do housework	4 (6)	17 (18)	47 (48)	<0.001
Visiting friends	1 (2)	7 (7)	27 (28)	<0.001
Read the newspaper	1 (2)	7 (7)	10 (10)	<0.001
Read a book	1 (2)	14 (14)	21 (22)	<0.001
Having visitors	1 (2)	8 (8)	22 (22)	<0.001
Moving around	2(3)	10 (11)	33 (34)	<0.001
Getting dressed	1 (2)	4 (4)	9 (9)	0.076
Performing daily care	0 (0)	5 (5)	8 (8)	0.059
Do the cooking	1 (2)	10 (10)	17 (17)	0.005
Do the shopping	1 (2)	10 (10)	35 (36)	<0.001
Watching TV	0 (0)	4 (4)	7 (7)	0.076
Practicing hobbies	2 (3)	10 (10)	25 (2)	<0.001

* N = never, S = sporadic, P = ‘persistent

Table 3.

Part A	**Variables significantly associated with sporadic fatigue (never as reference) in the sample (total n = 169)**					
Variables	**Univariate analysis**			**Multivariate analysis**		
	OR	**95%CI**	**P**	**OR**	**95%CI**	**P**
Not working	2.72	1.40 – 5.30	0.003	0.68	0.25 – 1.84	0.45
Working (reference)						
Disease course	2.40	0.84 – 6.90	0.10	1.88	0.50 – 7.11	0.35
RR/SP MS (reference)						
Use of medication	0.40	0.21 – 0.77	0.005	0.48	0.21 – 1.07	0.07
No use (reference)						
SF-36 PF	0.98	0.96 – 0.98	<0.001	0.97	0.96 – 0.99	0.004
Depression	1.23	1.12 – 1.35	<0.001	5.73	1.41 – 23.39	0.02
Insomnia	2.46	1.40 – 4.30	0.002	1.20	0.60 – 2.43	0.61
Suddenly fatigue	1.95	1.01 – 3.78	0.05	1.29	0.56 – 2.98	0.55
No (reference)						
Heat sensitivity	1.63	1.33 – 2.01	<0.001	1.31	1.02 – 1.70	0.04
No (reference)						
Part B	**Variables significantly associated with persistent fatigue (never as reference) in the sample (N= 166)**					
Variables	**Univariate analysis**			**Multivariate analysis**		
	OR	**95%CI**	**P**	**OR**	**95%CI**	**P**
Not working	5.23	2.65 – 10.33	<0.001	0.85	0.28 – 2.62	0.78
Disease course	4.61	1.67 – 12.74	0.003	3.11	0.67 – 14.52	0.15
Use of medication	0.44	0.22 – 0.86	0.016	0.52	0.18 – 1.56	0.24
SF-36 PF	0.95	0.94 – 0.97	<0.001	0.97	0.95 – 0.99	0.01
Depression	1.53	1.34 – 1.75	<0.001	52.95	8.54 – 328.40	<0.001
Insomnia	1.72	1.13 – 2.75	0.012	0.53	0.20 – 1.35	0.18
Suddenly fatigue	3.82	1.96 – 7.45	<0.001	2.38	0.87 – 6.54	0.09
Heat sensitivity	1.89	1.51 – 2.35	<0.001	1.50	1.07-2.12	0.02

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