Acta Neurologica Scandinavica
Acta Neurol Scand 2012: 126: 384–389 DOI: 10.1111/j.1600-0404.2012.01660.x

ACTA NEUROLOGICA SCANDINAVICA

Fatigue and heat sensitivity in patients with multiple sclerosis

Bol Y, Smolders J, Duits A, Lange IMJ, Romberg-Camps M, Hupperts R. Fatigue and heat sensitivity in patients with multiple sclerosis.
Acta Neurol Scand: 2012: 126: 384–389.

Objectives – Fatigue is one of the most common and troubling symptoms of multiple sclerosis (MS), and heat is often reported as a trigger. Although it is assumed that this heat sensitivity is specific for MS, the evidence for disease specificity is limited. We studied the relationship between fatigue, heat sensitivity, and environmental temperature, and its specificity for MS. *Materials and methods* – We compared 88 MS patients with 76 patients with ulcerative colitis (UC), another chronic auto-immune disease. As most important outcome measures, heat sensitivity, physical fatigue, mental fatigue, environmental temperature, and ambient UV-light levels were determined. *Results* – More patients with MS reported heat sensitivity for fatigue, compared to patients with UC (53.4% vs 35.5%, respectively, $P = 0.016$). However, heat-sensitive patients were equally fatigued as heat-insensitive patients. Climatological data, including day temperature and amount of ambient UV light, were not related to fatigue in both heat-sensitive and heat-insensitive patients with MS. *Conclusions* – Our findings support the assumption that heat sensitivity regarding fatigue has an MS-specific component. Although patients with MS experience a relationship between environmental temperature and fatigue, objective assessment by climatological data could not confirm this.

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Key words: fatigue; heat sensitivity; multiple sclerosis; temperature

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Accepted for publication February 3, 2012

Introduction

Fatigue is one of the most common and most disabling complaints in patients with multiple sclerosis (MS) (1). Compared with healthy controls and several other chronic somatic populations, fatigue in MS appears more frequently and is more severe (2–4). In addition, patients with MS often report specific triggers, such as heat (1, 5). About 58–93% of patients with MS experience a relationship between fatigue and environmental temperature (5–11), especially those with severe fatigue (7–9). Although it has been assumed that this heat sensitivity is specific for fatigue in MS, the evidence for disease specificity is limited (10, 11).

The focus of this study is on the relationship between fatigue, heat sensitivity, and environmental temperature and its specificity for MS. To assess the MS specificity of heat sensitivity, we compared MS patients with patients with ulcerative colitis (UC), an inflammatory bowel disease (IBD) that like MS is chronic, intermittent, and frequent in young adults (12). Both MS and UC are auto-immune diseases characterized by a lifetime risk of relapses and a compromising effect on physical, mental, and social well-being (13, 14). Fatigue is also a frequent and disabling symptom in patients with UC (15, 16). We expected that heat sensitivity is specific for fatigue in patients with MS, also when adjusted for fatigue severity. Firstly, we hypothesized that more patients with MS experience a relationship between fatigue and temperature/heat compared to patients with UC (subjective assessment of heat sensitivity). Secondly, we hypothesized that the environmental temperature is positively correlated with fatigue in MS patients and not in UC patients (objective assessment of heat sensitivity).

Materials and methods

Participants

Eighty-eight patients with MS and 76 sex- and age-matched patients with UC were included in this cross-sectional study (2). The patients with MS were recruited from the Department of Neurology of the Maastricht University Medical Centre (MUMC, Maastricht, the Netherlands). Consecutively referred patients who presented at the outpatients clinic, aged 18–60 years, and diagnosed with clinically definite MS (17, 18) were approached to participate in the study. Patients with UC who had been diagnosed using the Lennard-Jones criteria (18, 19) were selected from the IBD South Limburg database of the Department of Gastroenterology at the MUMC. MS and UC patients who had an exacerbation within the past 4 weeks and as such were in an active phase of their disease were excluded. Other exclusion criteria were as follows: a Kurtzke Expanded Disability Status Scale (EDSS) score >8 (18, 20); use of corticosteroids, somatic comorbidity, dementia or severe cognitive dysfunction and visual, verbal and/or motoric limitations interfering with filling out the questionnaires.

Procedure

All the participants were evaluated at the Department of Psychology of the MUMC, where they completed a battery of questionnaires. Fatigue was measured with the subscales physical and mental fatigue of the Multidimensional Fatigue Inventory (MFI) (18, 21). Both of these subscales consist of four items with a 5-point response format with scores ranging from 4 to 20. The MFI has been used in patients with chronic (neurological) diseases (2, 3, 15, 16, 22), and the Dutch language version has shown good reliability and validity (18, 21).

Heat sensitivity, defined as the experienced relationship between temperature and fatigue, was measured with two items of the Fatigue Assessment Inventory (11): 'Heat brings on my fatigue' and 'Cool temperatures lessens my fatigue'. Both items have a response format, ranging from 1 = completely disagree to 7 = completely agree with the statement. Patients were classified as heat sensitive if they had a score of ≥ 5 on both items and as heat insensitive as they have a score below 5 on both items. Because depression is often a confounding variable regarding fatigue in MS (2, 23, 24), depressive complaints were assessed by means of the depression subscale of the Hospital Anxiety and Depression Scale (HADS) (25). This subscale consists of seven items with scores ranging from 0 to 21. Reliability and validity have been proven good (26, 27).

Medical histories of the MS and UC patients (disease course and disease duration) were collected from the hospital database. The patients with UC completed the Colitis Activity Index (CAI) at inclusion (total score ranging from 0 to 18). The CAI is widely used as an outcome measure for monitoring the disease course. For the patients with MS, EDSS scores were collected from the hospital database. If there was no recent (>3 months before inclusion) EDSS score available, the treating neurologist was consulted for reassessment. Climatological data were obtained from the weather station of the Royal Netherlands Meteorological Institute in Maastricht (http://www.knmi.nl/climatology/daily_data/) and comprised mean and maximum day temperature (°C). As sunlight and vitamin D exposure have been reported to be beneficial in MS (28, 29), we also included estimates of these variables in the analysis. Data on the amount of ambient UV light in the Maastricht region were estimated with FastRT (Fast and easy UV simulation tool, version 2.3, Ola Engelsen, Norwegian Institute for Air Research, Tromsø, Norway) and comprised UV light within the erythematous spectrum and within the vitamin D synthesis spectrum (J/m^2) (30). This study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The medical ethics committee of the MUMC approved the project, and each participant gave informed consent.

Data analysis

Data analysis was performed using SPSS 16.0.1 for Windows (SPSS Inc., Chicago, IL, USA). Before analysis, data were checked for missing values, outliers, and normality. Square root transformation was performed where necessary. To compare disease severity between the groups, the MS disease severity (EDSS) was linearly transformed to the range of the CAI (2). Differences in MS/UC cohort characteristics were tested with independent samples *t*-tests. Differences between heat-sensitive and heat-insensitive subjects within the patient groups were examined with one-way ANOVA. Pearson's correlation coefficients were used to analyze interrelationships between demographic, clinical, and climatological data on the one hand and physical and mental fatigue on the other hand. Chi-square analysis was used to compare the proportion of heat-sensitive subjects in both patient groups. Heat sensitivity in both patient groups was compared by means of a logistic regression analysis using a forced entry method with heat sensitivity as outcome measure and age, sex, type of disease, disease duration, disease severity, depression, physical fatigue, and mental fatigue as predictor variables. Beforehand, multicollinearity was assessed by means of the variance inflation factor (VIF) and associations among the predictor variables. For the logistic regression analyses, results were expressed as odds ratios (OR) with 95% confidence intervals (95%CI). *P*-values of <0.05 were considered significant for all analyses.

Results

Participants

Most of the patients with MS (66%) had a relapsing remitting disease course, 18% had secondary progressive MS, and 16% had primary progressive MS. In the MS group, the average EDSS score was 3.5 (SD = 1.9, range 0–7.5). In the UC group, the average CAI score was 3.5 (SD = 2.1, range 0–9). All other patients' characteristics and climatological data are presented in Table 1.

Subjective assessment

A higher proportion of the patients with MS (53.4%) were classified as heat sensitive regarding fatigue compared to the patients with UC (35.5%) [χ^2 (1, n = 164) = 5.267, P = 0.016]. No differences were found in physical and mental fatigue between heat-sensitive and heat-insensitive subjects in both patient groups. Table 2 shows the logistic regression model predicting heat sensitivity with the demographic and clinical characteristics as independent variables. The overall model was significant [χ^2 (8, n = 164) = 16.387, P = 0.037 Nagelkerke R^2 = 0.127]. Patients with MS were more likely to be heat sensitive when compared to patients with UC (OR = 4.462, 95%CI = 1.824–10.912, P = 0.001). Heat sensitivity was also explained by longer disease duration (OR = 1.455, 95%CI = 1.046–2.025, P = 0.026) and decreasing disease severity as expressed by EDSS and CAI scores (OR = 0.836, 95%CI = 0.728–0.960, P = 0.011). Sex, age, depression, physical fatigue, and mental fatigue did not contribute to heat sensitivity.

Table 1 Characteristics [mean and (SD)] of both patient groups

	Multiple sclerosis (N = 88)	Ulcerative colitis (N = 76)
Sex (% male/% female)	30/70	32/68
Age (years)	43.6 (9.0)	45.3 (8.8)
Disease severity[A]	6.4 (3.5)	3.5 (2.1)*
Disease duration (years)	5.7 (6.2)	10.1 (7.0)*
Physical fatigue	14.4 (3.7)	11.1 (4.8)*
Mental fatigue	12.3 (4.6)	9.7 (4.6)*
Depression	5.6 (4.0)	4.0 (3.6) *
Mean day temperature (°C)	9.8 (6.8)	10.6 (6.9)
Maximum day temperature (°C)	13.6 (7.9)	14.5 (7.7)
UV Erythematous dose (J/m^2)	67.7 (54.0)	69.3 (48.2)
UV Vitamin D effective dose (J/m^2)	112.4 (102.5)	116.6 (95.5)

[A]Because of the different range of both disease severity measures, the scores of the multiple sclerosis disease severity measure (EDSS) were linearly transformed into the range of the CAI (0–18) for reasons of comparison (2).
*$P < 0.01$ (two-tailed).

Table 2 Logistic regression model predicting heat sensitivity

	Heat sensitivity	
Variable	OR	95%CI
Sex	1.425	0.671–3.027
Age	0.995	0.957–1.034
Disease duration	1.455*	1.046–2.025
Disease severity	0.836**	0.728–0.960
Depression	0.993	0.892–1.105
Disease[A]	4.462**	1.824–10.912
Physical fatigue	1.033	0.932–1.145
Mental fatigue	1.013	0.928–1.106

[A]Ulcerative colitis = 0, multiple sclerosis = 1.
*$P < 0.05$; **$P < 0.01$ (two-tailed).
OR, odds ratio, 95%CI, 95% confidence interval.

Objective assessment

Correlations between climatological data and fatigue are shown in Table 3. None of the climatological variables was significantly correlated with physical and mental fatigue in both patient groups

Table 3 Pearson correlations of climatological measures with fatigue in both patient groups

	Multiple sclerosis (n = 88)		Ulcerative colitis (n = 76)	
	Physical fatigue	Mental fatigue	Physical fatigue	Mental fatigue
Mean day temperature	−0.046	0.046	−0.137	−0.101
Max day temperature	−0.027	0.053	−0.150	−0.153
UV erythematous dose	0.000	0.000	−0.176	−0.139
UV vitamin D effective dose	0.015	0.005	−0.173	−0.133

*$P < 0.05$; **$P < 0.01$ (two-tailed).

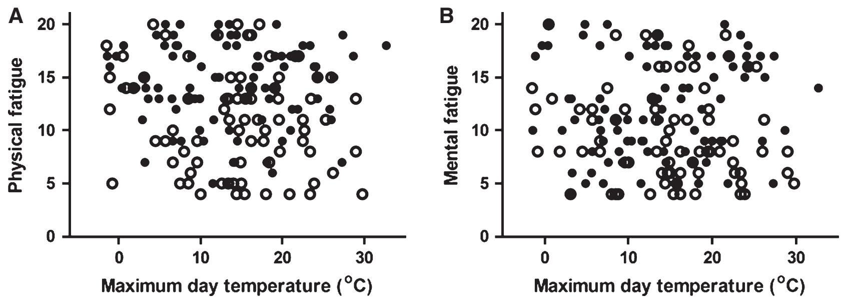

Figure 1. Fatigue and maximum day temperature in multiple sclerosis (MS) and ulcerative colitis (UC) patients. Scatterplot of correlations between temperature and physical fatigue (A), and between temperature and mental fatigue (B). Symbols: •, MS patients; ○, UC patients.

(Fig. 1). Additionally, stratification of both cohorts in heat-sensitive and heat-insensitive subjects did not reveal any evidence of a positive correlation between environmental temperatures and fatigue (Table S1). Interestingly, the heat-insensitive UC subjects appeared to be less-fatigued with increasing temperatures, in contrast with their MS and heat-sensitive UC counterparts.

Discussion

To study the relationship between fatigue, heat sensitivity, and environmental temperature and its specificity for MS, we compared MS patients with UC patients. In line with our hypothesis, a greater proportion of MS than patients with UC reported heat sensitivity for fatigue (53.4% vs 35.5%). The regression analysis revealed that this difference was not attributable to differences in disease severity, disease duration, level of fatigue, or level of depression. However, we could not find any correlation of environmental temperature with the levels of mental and physical fatigue reported in both cohorts. Although the prevalence of heat sensitivity in relation to fatigue is higher in patients with MS than in UC, fatigue is not associated with environmental temperature.

The prevalence of heat sensitivity as found in the present MS sample is relatively low in comparison with other studies with percentages varying between 58% and 93% (5–11). Additionally, heat-sensitive patients are equally fatigued as heat-insensitive patients, which is in contrast with earlier findings (7–9). Several factors may explain these differences, including the use of different instruments to assess fatigue and different ways to classify patients as heat sensitive. Also the inclusion of depression as a covariable in our study could be an explanation of the contrasting results. Depression is very common in MS and an important confounder in fatigue studies (2, 23, 24). Interestingly, in our study, a longer disease duration of both MS and UC corresponded with a larger likelihood of reporting heat sensitivity, as did a lower level of mobile impairment and physical complaints (EDSS and CAI). We can only speculate about the drivers of these associations, but at least they do not explain the reported difference in the prevalence of heat sensitivity between MS and UC patients.

Although heat sensitivity was reported by the participants, we were unable to detect a correlation between the level of their reported fatigue and environmental temperature. This seems contradictory, because 53% of the studied patients with MS report such a relationship, as well as patients with MS in previous studies (5–11). Possibly, the temperatures in the range which we measured were too low to affect the fatigue level of participants significantly. Studies between patients with MS in warmer climates may yield different results. Additionally, the cross-sectional design does not allow monitoring of a longituidinal relationship between fatigue and temperature in individual participants. Possible confounders including outdoor activities and heath-avoiding behavior were also not assessed in our study. Interestingly, however, heat-insensitive patients with UC reported less fatigue with increasing temperatures, in contrast with their heat-insensitive MS counterparts. This may point toward a difference in the relationship between fatigue and environmental temperature between MS and UC patients. However, our study does not provide the data to further explore such a difference. Ambient UV exposure within both the erythematous and vitamin D effective spectrum did also not correlate with the level of fatigue reported. This is in accordance with an earlier study, in which we found no correlation between vitamin D status in the circulation and level of fatigue in a cohort of patients with MS (31). As sunlight is the most important promoter of vitamin D synthesis in the human body, the claimed positive effect of vitamin D on fatigue in other diseased cohorts appears the opposite of heat sensitivity in relation to fatigue (32). As neither temperature, nor UV exposure was correlated with the level of fatigue in our cohorts, we were unable to shed more light on this apparent paradox.

Our data suggest that specifically patients with MS are more prone to be heat sensitive regarding fatigue when compared to patients with UC. The mechanism underlying this MS-specific component is uncertain. The temporary worsening of neurological symptoms in MS caused by an increase in temperature is known as the Uhthoff's phenomenon (33). This phenomenon was first described by Wilhem Uhthoff in 1890 as a temporary worsening of vision with exercise in patients with optic neuritis. Later work revealed the link between exercise and increased heat production. Uhthoff's phenomenon is the result of an increase in body temperature (hyperthermia) that can in turn be caused by exercise, hot baths, or showers. One explanation of Uhthoff's phenomenon is that hyperthermia induces a heat-linked neuro-blockade of partially demyelinated axons. Other theories suggest that heat itself effects serum calcium, blockade of ion channels, circulatory changes, heat shock proteins, and unidentified humoral substances (33). Alternatively, as during fever, increased body temperature induces molecular changes in T lymphocytes, possibly exaggerating the auto-immune response in MS (34). The relative contribution of environmental temperature to core body temperature is, however, limited. A disturbed thermoregulation in patients with MS because of thalamic lesions has also been proposed to contribute to specific heat sensitivity in MS (8). Alternatively, we cannot exclude that the higher prevalence of heat sensitivity may be due to a report bias, because a negative effect of heat sensitivity on MS symptoms is a well-known phenomenon.

To the best of our knowledge, this is the first study that focused on the relationship between climatological data and the experience of physical and mental fatigue and heat sensitivity. We reproduced the increased prevalence of heat sensitivity among patients with MS, but could not find a correlation between temperature and physical/mental fatigue in MS.

Acknowledgements

The authors have no acknowledgements to declare.

Conflict of interest

The authors declare that they have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1. Pearson correlations of climatological measures with fatigue in the (a) MS and (b) UC group.

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