Sensitivity to increased temperature in individuals with Multiple Sclerosis: a key symptomatic factor shown in a survey

Abstract

Background: Many individuals diagnosed with Multiple Sclerosis (MS) are sensitive to increased body temperature, which has been recognized to correlate with the symptom of fatigue. The need to investigate this association has been highlighted. The aim of the study was to investigate the occurrence of heat sensitivity and its relations to disease course, disability, common MS-related symptoms and ongoing immunosuppressive treatments among individuals 65 years or younger diagnosed with MS.

Method: A cross-sectional designed survey was undertaken. A questionnaire was sent to MS-patients with an Expanded Disability Status Score (EDSS) in the interval 0-6.5 and who were between 20 and 65 years of age, living in an eastern region of Sweden (n=334). Besides occurrence of heat sensitivity (Yes/No) and corresponding questions, the Fatigue Severity Scale (FSS), the MS-related symptom checklist and the Perceived Deficit Questionnaire (PDQ) was included. Data were analysed in relation to data level by Chi-square, Mann Whitney U-test, and Student’s t-test. Pearson’s and Spearman’s correlations were calculated. In logistic regression analyses (enter) dichotomized MS-symptoms were used as dependent variables, and EDSS, disease-course, heat-sensitivity, age and sex (female/male) were independent variables. In linear regression analyses, enter, summated FSS and PDQ were entered as dependent variables and EDSS, disease-course, heat-sensitivity, age and sex (female/male) were independent variables.

Results: Of the responding patients (n=256), 58% reported heat sensitivity. The regression analyses revealed heat sensitivity as being a significant factor correlating not only with fatigue (p<0.001), but also with several other common MS symptoms such as pain (p<0.001), concentration difficulties (p<0.001), and urination urgency (p=0.009).
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Discussion/Conclusion: The findings are discussed in relation to hypothesized explanations which need further investigation.

Keywords: concentration difficulties; cross-sectional study; depression; fatigue; pain; questionnaire
**Background**

Between 60 and 80% of individuals diagnosed with the neurological disease Multiple Sclerosis (MS) have been reported as being sensitive to environmental heat [1]. Clinically, increased body temperature can result in increased neurological signs and MS symptoms. Blurred vision, known as Uthoff’s phenomenon and first described in 1890, is caused by increased body temperature due to physical exercise or physical restraint [2]. The body temperature is found to influence nerve impulses, which are blocked or slowed down in a damaged nerve [3-5]. After normalization of the temperature, signs and symptoms improve or disappear [1-2].

Heat sensitivity has been described as a significant correlate of the symptom of fatigue in MS [3, 6-8]. Together with divided attention and reduced muscular endurance, both heat sensitivity and fatigue have been reported as predictors of accidental falls [9]. Recently, Marino [4] stressed that heat sensitivity has been disregarded in studies focusing on fatigue.

In studies covering several decades, the occurrence rate of fatigue among individuals with MS is described as from 60 to more than 90% [3, 10-12]. Although treatment options can slow the disease trajectory, a majority of individuals with MS still report fatigue as their main problem and their most debilitating symptom [12-14].

Irrespective of disease course, already in 1984 Freal and co-workers [3] reported fatigue as the very first symptom in about a third of patients. This initial symptom has been found to persist over the disease trajectory. In a follow-up study covering two years, 27% of 219 individuals reported persistent fatigue, while 19% reported non-persistent fatigue during the period [15]. In another longitudinal study (n=228) covering ten years, 96
individuals participated in a second data collection [16], and of those who had scored severe fatigue at baseline (n=68) 74% still remained fatigued. Unfortunately, none of the latter studies focused on heat sensitivity, although its correspondence between disease severity and fatigue needs to be addressed.

During recent decades, individuals diagnosed with MS have had increased opportunities for treatment through the development of immune-modulating medications. These products affect the frequency of relapses and slow the progression of disability. Some immune-modulating products (e.g. beta-interferon) have side effects of influenza-like symptoms and fatigue, and may also increase depressive symptoms [17]. However, in treatment with beta-interferon, the initial side effects of influenza-like symptoms and perceived fatigue often decrease when the treatment spans a longer period. Another product, glatiramer acetate, is clinically considered neutral in this respect [18]. A relatively new immune-modulating product (natalizumab) has been reported to decrease the symptom of fatigue [19].

The aim of this study was to investigate the occurrence of heat sensitivity and its relations to disease course, disability, common MS-related symptoms (especially fatigue), and ongoing immunosuppressive treatments among individuals 65 years or younger diagnosed with MS and living in an eastern county of Sweden.

**Methods**

**Study group**

In order to reach individuals diagnosed with MS living in the area, a cross-sectional designed survey was undertaken, addressed to the individuals registered in the Swedish MS register
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Together with information about the study, a questionnaire and a pre-paid reply envelope were mailed to 334 individuals fulfilling the following criteria: i) being diagnosed with MS, ii) having an Expanded Disability Status Score (EDSS) [20] in the interval 0≤EDSS≤6.5, and iii) being of working age, i.e. 20-65 years, as 65 years is the official retirement age. The questionnaires were distributed during 2007 to individuals with EDSS 1-6.5, and a complementary distribution was sent to individuals EDSS=0 in 2008. To those who had not answered within three weeks, one reminder was sent.

Data collection

The individual’s name, age, sex, disease course and function, measured with the EDSS [20], together with date of onset of MS, were obtained from the SwMS register. Common background factors, such as civil status, family, level of education and ongoing medical treatment, were requested in the questionnaire. Occurrence of heat sensitivity (Yes/No) and related questions, together with occurrence and severity of fatigue, were requested as well. Furthermore, the following instruments were included: the Fatigue Severity Scale (FSS) [6, 10]; the MS-related symptom checklist [21], and the Perceived Deficit Questionnaire (PDQ) [22].

In this study, and based on earlier studies [11, 15, 23], the EDSS was grouped according to normal neurological condition (EDSS=0), mild disability (1.0≤EDSS≤3.5), moderate disability (4.0≤EDSS≤5.5), and severe disability (6.0≤EDSS≤6.5).

The FSS [6, 10] comprises nine items covering perceived severity of fatigue, and each item is graded from least fatigue (1) to severe fatigue (7). The summated score varies from 9 to 63; the higher the score, the more severe the perceived fatigue. As in earlier studies [e.g.
in this study an FSS mean score ≤4 was regarded to indicate no fatigue, >4 but <5 indicated borderline fatigue, and ≥5 was regarded to indicate severe fatigue. The FSS has been used in earlier studies in Sweden [15] and is also used clinically. In this study, concurrent validity was assessed through correlations between the FSS total with questions about the impact of fatigue on daily life as well as the occurrence of fatigue, rated on the MS-related symptom checklist [21], and resulted in $r = 0.79$ (P<0.01) and $r = 0.77$ (P<0.01), respectively. Reliability was assessed using Cronbach’s alpha, and the alpha coefficient was 0.93.

The MS-related symptom checklist [21] was used to report 25 common MS symptoms such as fatigue, weakness in arms and legs, balance problems, pain, numbness, blurred vision, depression, and difficulties with urination such as frequency and urgency. The occurrence of each symptom is graded in six steps from never (1) to always (6). In this study, the data were treated as dichotomized into never/sometimes and usually/always. The checklist has been found to be closely related to EDSS [21], and has also been used in an earlier study in Sweden [12].

Cognitive dysfunction was assessed using the PDQ [22], measuring perceived problems with memory, attention and concentration. The original English version of the PDQ was translated into Swedish and then back-translated in accordance with Streiner and Norman [25], with good agreement. Twenty items are graded from never (0) to always (4). Summated score vary from 0 to 80, where higher scores indicate greater cognitive problems. In this study, concurrent validity, assessed through correlations between the PDQ sum score and the MS-related symptoms forgetfulness and concentration difficulties, was $r=0.75$
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(P<0.01) and r=0.73 (P<0.01), respectively. Reliability was tested using Cronbach’s alpha (0.95) and the split-half technique (r=0.87).

**Statistical analyses**

The data have been treated and analysed in relation to perceived heat sensitivity. The descriptive statistics used are in congruence with measurement scale level, except for the FSS which is treated on interval level as in earlier studies [e.g. 10, 15, 24]. Differences between groups have been tested with the chi-square test on data on nominal level, with the Mann Whitney U-test on data on ordinal level, and with Student’s t-test on data on interval level. To test associations between variables, Pearson’s and Spearman’s correlations were calculated. In the logistic regression analysis, enter, those MS symptoms that were significantly more frequent among heat-sensitive participants were dichotomized and entered as dependent variables, and EDSS (0-6.5), disease course (relapsing/progressive forms), heat sensitivity (yes/no), and age and sex (female/male) were independent variables. In the linear regression analysis, enter, summated FSS and PDQ were entered as dependent variables and EDSS (0-6.5), disease course (relapsing/progressive forms) and heat sensitivity age and sex were independent variables. In all analyses, a P-value <0.05 has been considered a significant value.

**Ethical considerations**

The study was guided by common ethical principals in research and according to the Declaration of Helsinki [26]. Approval to use the SwMS register was received from the responsible local administrator. The Regional Ethical Review Board at the Faculty of Health
Sciences, Linköping University, Sweden (Dnr M13-07) also approved the study. A completed and returned questionnaire was considered received informed consent.

Results

Study group

Two hundred and fifty-six patients, 195 (76%) women and 61 (24%) men, 65 years or younger and with an EDSS score between 0 and 6.5, answered the questionnaires. The response rate was 79.3%. Between participants and non-participants there were no statistically significant differences regarding sex ($P=0.052$), disease course ($P=0.664$) or EDSS score ($P=0.142$). The non-participants were about five years younger than the participants, $m=42.7$ years, (SD 10.5) ($P<0.001$) and also had significantly fewer years with MS since debut, $Md=10$ ($Q_1=5.75; Q_3=15.25$) ($P=0.014$). (Table I).

Of the participants, the women were significantly older ($P=0.022$) than the men, 48.3 (SD 11) and 44.8 (SD 10.1), respectively. At debut the median age was 31 years ($Q_0=25; Q_3=38$). In 5.5% of the participants, debut occurred before 20 years of age, and the youngest had been 12 years old. The main course of the disease was relapsing-remitting (73%). Ten percent had an EDSS score of 0, but most of the patients (61%) had a mild disease severity according to the EDSS. Seventy-nine percent of the participants were being treated pharmacologically, and of those, 71% were being treated with immune modulating medication and 13% reported taking medication for fatigue (Table I).

[Please, insert Table 1 about here]

Heat sensitivity
One hundred and forty-nine participants (58%) reported heat sensitivity, with no difference between women and men ($P=0.102$) or in relation to disease course ($P=0.226$). More heat-sensitive participants had higher EDSS scores ($P=0.02$). In the interval $1 \leq \text{EDSS} \leq 3.5$, 62% of 157 participants were sensitive to heat. In the interval $4.0 \leq \text{EDSS} \leq 5.5$, 53% of 30 participants were sensitive to heat. In the interval $6.0 \leq \text{EDSS} \leq 6.5$, 63% of 43 participants reported heat sensitivity. Of those who were sensitive to heat, 70% preferred a room temperature of less than 20°C, while 73% of those who were not heat sensitive preferred a room temperature of more than 20°C ($P<0.001$). Eleven of the heat-sensitive participants ($n=149$) annotated in the questionnaire that they also were ‘cold’.

Of common MS-related symptoms, the heat-sensitive participants reported a significantly higher occurrence of several symptoms than the participants who were not heat sensitive, for example fatigue, weakness in legs, concentration difficulties, pain, and urination urgency (Table II). Weakness in arms and legs as well as balance problems correlated significantly with the EDSS, $r=0.17$ ($p<0.01$), $r=0.49$ ($p<0.01$), $r=0.51$ ($p<0.01$), respectively.

[Please, insert Table II about here]

In the logistic regression analysis, heat sensitivity significantly predicted several MS symptoms, such as fatigue, concentration difficulties and pain. Two of the symptoms, spasms and balance problems, were explained by the EDSS alone (Table III) while some were explained by more than one variable. Together with heat sensitivity and the EDSS, increasing age also explained the occurrence of weakness in arms (OR=$1.05$, 95%CI=$1.02$-$1.08$, $P=0.001$), weakness in legs (OR=$1.03$, 95%CI=$1.0$-$1.06$, $P=0.042$), pain (OR=$1.04$, 95%CI=$1.0$-
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1.07, \( P=0.025 \), and urination frequency (OR=1.04, 95%CI=1.04-3.07, \( P=0.007 \)). Urination urgency was also explained by gender, female (OR=0.23, 95%CI= 0.07-0.7, \( P=0.01 \)). The symptom of falling was predicted by gender, male, alone (OR=3.11, 95%CI=1.11-8.74, \( P=0.032 \)). Finally, sexual difficulties were predicted by both age (OR=1.03, 95%CI=0.85-2.89, \( P=0.044 \)) and gender, male (OR=2.08, 95%CI=1.07-4.03, \( P=0.03 \)).

The difference in the occurrence of fatigue was confirmed by the FSS. The heat-sensitive participants had a summated FSS score Md=49 (Q1=40.5; Q3=56) and the non-heat-sensitive participants Md=38 (Q1=23; Q3=47; \( P<0.001 \)). Of those who were heat sensitive, 63% reported severe fatigue, FSS≥5, while among those who were not heat sensitive 45% reported mild or no fatigue, FSS≤4, \( (P<0.001) \) (Table IV). One hundred and ten (57%) of the women (n=192) and 21 (35%) of the men (n=60) scored an FSS mean value ≥5, classified as fatigued (\( P=0.010 \)). About a third of the participants who were heat sensitive had concentration difficulties significantly more often (\( P<0.001 \)). This difference was confirmed by the PDQ, with Md=29.5 (Q1=19; Q3=38) among the heat-sensitive participants and Md=21 (Q1=12; Q3=33) in the non-heat-sensitive participants (\( P<0.001 \)). In the linear regression analyses, heat sensitivity predicted both fatigue and concentration difficulties (Table V).

There was no difference between heat-sensitive and non-heat-sensitive participants in the use of immune-modulating drugs or treatment for fatigue. Of those being treated with the immune-modulating beta-interferon, significantly fewer reported severe fatigue, FSS≥5.0, compared to those being treated with glatiramer acetate or natulizumab (\( P=0.021 \)).
Of those who were being treated for fatigue with modafinil (n=32), a significantly higher proportion reported severe fatigue, FSS≥5.0 (P=0.016), compared to those who were not being treated for fatigue.

**Discussion**

This study is an explorative study aimed at investigating the occurrence of heat sensitivity in a group of individuals diagnosed with MS. Further, it aimed to investigate relations between heat sensitivity and common symptoms in MS, disease course and disability. Our results indicate that heat sensitivity is highly correlated with several symptoms commonly reported by MS patients. That heat sensitivity is associated with fatigue is well known, reported by several authors previously [3, 6-8]. However, our data also reveal that heat sensitivity is a key factor associated with the occurrence of a wide variety of other MS symptoms, for example pain, concentration problems and urination urgency.

*Heat sensitivity intensifies MS symptoms*

The most striking result in this study is that heat sensitivity significantly correlated with - and in the logistic regression analyses, appeared as an explaining factor for - the most incapacitating symptoms of MS, viz. fatigue, concentration problems and pain. This result discloses heat sensitivity as a key clinical factor. Our findings are consistent with a Norwegian study by Nortvedt and co-workers, stating that the most problematic symptoms of MS, with a significant impact on quality of life, are bodily pain and low vitality [27], which are strongly related to the symptom of fatigue [24].
We found that many other MS symptoms are also correlated with heat sensitivity. Interestingly, similar observations were actually reported in the early works of Uthoff, although subsequent citations narrowed the interpretation of Uthoff’s phenomenon to blurring of the vision [4]. In the present study, however, no relationship between the symptom of blurred vision and heat sensitivity was confirmed.

What might be the cause of the observed co-occurrence of heat sensitivity and pain, fatigue and cognitive problems? Can this indicate something about the pathogenic mechanism? Central pain in MS seems to be generated through lesions affecting the spinothalamo-cortical pathways [28], and a third of the MS patients with central pain had visible lesions in the thalamus [29]. One may speculate that the thalamus might be involved. It is also interesting to think about the effects of decreased sweating in terms of electrolytic imbalance and secondary neuronal effects. Recent results by Saari and co-workers [33] disclose such impairment in thermoregulatory sweating in MS. One idea that may explain thermoregulatory dysfunction is that lesions can affect important cerebral areas such as the hypothalamus. The study by Saari [30] also demonstrated a correlation between increasing sweating impairment and increasing disability (EDSS), which is congruent with our results of a correlation between heat sensitivity and increasing EDSS.

Fatigue in MS has been eagerly studied by many researchers during the past decade. Fatigue and heat sensitivity are related in many aspects, and a subsequent question is whether they have common pathogenic features. Recently, Marino [4] stated that MS fatigue is likely to be a central rather than a peripheral phenomenon. Heat sensitivity in MS, however, is not understood as clearly.
The mechanism behind heat sensitivity

The mechanism of heat sensitivity in MS is reviewed in a recent article by Marino [4]. The heat reaction blocks the action potential of the demyelinated neuron (frequency-dependent conduction block - FDCB) [5]. The demyelinization results in a slower nerve conduction velocity. A conduction block can occur because the damaged axons transmit only single or low frequency impulses, instead of high frequency impulse trains like in healthy nerve tissue [31]. Marino [4] states that this observation is very important, especially when an increase in temperature blocks nerve impulses in demyelinated fibres [32]. Interestingly, very small increases in temperature can also block action potentials [5]. The heat sensitivity in MS is described by Baker as secondary to both environmental heat and environmental humidity as well as to exercise [33]. Both passive and active body temperature increases give heat reactions. Clinical reports from individual patients in our MS clinic (i.e. outside this study) reveal that their experience of temperature aberrations can vary greatly, indicating that the mechanisms may be multiple.

The subjective phenomenon of heat sensitivity

Many patients with MS are aware of their heat sensitivity, and have experienced increased clinical symptoms when they became warm from fever, hot environmental temperature or physical exercise. In this study, patients who did or did not report heat sensitivity were dichotomized and analysed according to this categorization. It is worth noting that some patients reported both heat sensitivity and a subjective feeling of “cold”. This suggests that temperature aberrations in MS can be complex and individual. In our clinical practice we also
encounter MS patients with complex subjective temperature aberrations, e.g. patients who deny heat sensitivity when asked, yet prefer to sleep in cold bedrooms because it alleviates their MS symptoms. Such patients may not yet be aware of a mild heat sensitivity. This factor also suggests that milder forms of heat sensitivity may be underreported in a study like ours. We have also met one patient who likes to be in the sun all day without any side effects, but when jogging has to take repeated showers to prevent incapacitating fatigue. Finally, it is well known that patients with severe MS can sometimes develop hypothermia, often without any major subjective symptoms. We suggest that qualitative studies should be initiated to describe patients’ experiences of a subjective phenomenon like heat sensitivity, feeling cold and combinations. One cannot exclude that central and peripheral mechanisms interact in the “temperature syndrome” of MS, which includes more features than the classical heat sensitivity.

_Fatigue as a side effect of immune modulating drugs_

It has recently been suggested that beta-interferon can increase fatigue through influenza-like side effects including hyperthermia, but that glatiramer-acetate, on the other hand, is a neutral agent in this respect, and that natalizumab at least in some cases decreases fatigue. Some scientific reports support these observations [17-19]. In our study, however, none of these relationships could be demonstrated. Another observation in our study was that a majority of those patients who were receiving treatment for fatigue still reported severe fatigue.
In conclusion, although heat sensitivity in MS was described as early as the late 19th century and is a well-known phenomenon today, it has to date been disregarded in studies of fatigue in MS [4]. The findings in this study underline the importance of heat sensitivity in MS patients as a key symptom that is highly correlated with disabling symptoms such as fatigue, concentration difficulty, and urination urgency. A majority of the participants rated the symptom of fatigue as their most impairing symptom. Furthermore, a significantly higher proportion among the heat-sensitive participants rated higher levels of fatigue compared to the participants who were not heat sensitive.

The results of our study put heat sensitivity in the position of a key clinical symptom. Our findings emphasize the need to further investigate the mechanism of heat sensitivity: What is the role of the sweating impairment? Is there thalamic involvement? What is the role of the immune system? One should also analyse what it means for patients and in the care of MS patients. Finally, a challenging topic to investigate is how heat sensitivity can be treated clinically, for example using thermotherapy.
Heat sensitivity in MS influences symptoms

References


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Additional files provided with this submission:

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