

Elevated body temperature is linked to fatigue in an Italian sample of relapsing–remitting multiple sclerosis patients

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Abstract Elevated body temperature was recently reported for the first time in patients with relapsing–remitting multiple sclerosis (RRMS) relative to healthy controls. In addition, warmer body temperature was associated with worse fatigue. These findings are highly novel, may indicate a novel pathophysiology for MS fatigue, and therefore warrant replication in a geographically separate sample. Here, we investigated body temperature and its association to fatigue in an Italian sample of 44 RRMS patients and 44 age- and sex-matched healthy controls. Consistent with our original report, we found elevated body temperature in the RRMS sample compared to healthy controls. Warmer body temperature was associated with worse fatigue, thereby supporting the notion of endogenous temperature elevations in patients with RRMS as a novel pathophysiological factor underlying fatigue. Our findings highlight a paradigm shift in our understanding of the effect of heat in RRMS, from exogenous (i.e., Uhthoff's phenomenon) to endogenous. Although randomized

controlled trials of cooling treatments (i.e., aspirin, cooling garments) to reduce fatigue in RRMS have been successful, consideration of endogenously elevated body temperature as the underlying target will enhance our development of novel treatments.

Keywords Multiple sclerosis · Temperature · Fatigue

Introduction

Uhthoff's observation in 1890 revealed the negative consequences of heat exposure for multiple sclerosis (MS) patients [1]. Experimental work in the intervening 125 years has elucidated many ways in which MS patients are negatively impacted by heat exposure. However, only recently, elevated body temperature outside of experimental manipulation was reported in relapsing–remitting MS (RRMS) patients (relative to healthy persons) [2]. That is, body temperature in RRMS patients was shown to be elevated at rest, i.e., endogenously. Moreover, warmer body temperature in these patients was clinically meaningful, as it was associated with worse fatigue. A prominent, pervasive, and debilitating symptom experienced by nearly all MS patients, fatigue remains poorly understood and we currently lack effective treatments for it. Although stimulant medication is frequently prescribed to treat MS fatigue, randomized controlled trials have failed to support their efficacy. In contrast, treatments such as cooling garments and aspirin have been shown to effectively reduce fatigue in MS [3–5].

Given the novelty of our body temperature–fatigue findings, we sought to replicate them in an independent, geographically distinct RRMS sample. Here, we examine body temperature and its relationship to fatigue in a sample

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of RRMS patients and age-matched healthy controls from a hospital-based MS center in Milan, Italy.

Methods

This study was approved by the ethical review board of University Hospital San Raffaele, Milan. All participants provided written informed consent before enrollment.

Participants

44 patients with RRMS and 44 age- and sex-matched healthy controls served. Mean age of RRMS patient group was 37.8 ± 12.5 years, and mean age of healthy controls was 38.5 ± 14.0 years ($P = 0.80$). Patient group comprised 24 females and 20 males; control group comprised 30 females and 14 males ($P = 0.193$). Patients had mean disease duration of 10.8 ± 7.8 years.

Body temperature

Consistent with our prior study, body temperature was recorded aurally with an infrared thermometer (Braun ThermoScan IRT 4520). Test–retest reliability of measurements with this thermometer as established in our original sample was high ($r = 0.78$). (Note: three participants were administered interferon; all had body temperature measured prior to injection).

Fatigue

Fatigue was assessed in a representative subsample of 37 RRMS patients with two widely used, reliable measures of fatigue in MS: the fatigue severity scale (FSS) [6] and the modified fatigue impact scale (MFIS) [7]. Consistent with our previous work [2], we examined cognitive fatigue (MFIS-C) and physical fatigue (MFIS-P) subscales of the MFIS separately. Because self-reported fatigue increases with age and depression (an effect which is shown to persist over time) [8], fatigue scores were regression-adjusted for age and depressive symptomatology (Montgomery–Asberg depression rating scale [9] to control for mood-related aspects of self-reported fatigue).

Statistical analyses

Body temperature differences between RRMS patients and healthy controls were evaluated with an independent samples t test. Next, to investigate the association between fatigue and body temperature in RRMS, correlations were run between body temperature and self-reported fatigue for the FSS, as well as MFIS-C and MFIS-P subscales of the

MFIS. Given the confirmatory study design, one-tailed tests were employed. We predicted that (1) RRMS patients have elevated body temperature relative to healthy controls and (2) elevated body temperature is associated with worse self-reported fatigue on the FSS, with a specific relationship to physical fatigue (MFIS-P) rather than cognitive fatigue (MFIS-C) subscale of the MFIS, consistent with our previous report [2].

Results

Body temperature

Body temperature was higher in RRMS patients (mean $\pm$ SD $37.06 \pm .26$ °C) relative to healthy controls (mean $\pm$ SD 36.89 ± 0.31 °C), $t(86) = -2.80$, $P = 0.003$ (see Fig. 1).

Fatigue in RRMS patients

Elevated body temperature in patients with RRMS was associated with higher self-reported fatigue on the FSS ($r = 0.274$, $P = 0.050$) and the MFIS-P ($r = 0.293$, $P = 0.039$), but not the MFIS-C ($r = 0.188$, $P = 0.133$). These findings are consistent with our original report in a separate sample of RRMS patients.

Discussion

Consistent with our original sample collected in the Northeastern US, body temperature was elevated in this Italian sample of RRMS patients relative to healthy controls. Furthermore, and also consistent with our prior finding, higher body temperature was associated with

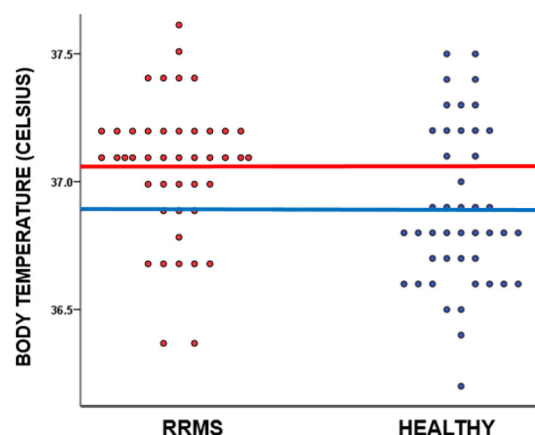


Fig. 1 Mean body temperature in RRMS (red) = 37.06 °C $\pm$.26, in healthy controls (blue) = 36.89 °C $\pm$.31

worse fatigue. Our findings support elevated body temperature in RRMS as a candidate disease marker with clinically meaningful implications, namely its association to fatigue. Understanding fatigue is an urgent MS research priority, given the paucity of effective treatments at present. Shifting our focus from arousal dysfunction to elevated body temperature as an underlying cause of fatigue supports the use of cooling/antipyretic treatments already shown to be effective for reducing fatigue in MS.

Elevated body temperature may signify clinically silent inflammatory activity taking place in the brains of persons with RRMS (for discussion, [10]). This hypothesis is supported by recent evidence showing elevated brain temperature in RRMS patients compared to healthy controls [11, 12]. Future research is needed to establish the relationship of elevated brain temperature to fatigue in persons with RRMS. Positive findings would support the development of novel body/brain cooling treatments for fatigue in MS. And, given the likelihood of multiple etiologies underlying MS fatigue, it will also be important to identify patients with elevated body/brain temperature as those most likely to benefit from these treatments.

Finally, our findings may hold implications for clinical populations beyond MS and our understanding of the impact of body temperature on fatigue more broadly. For example, anti-inflammatory treatments (e.g., NSAIDs) have been found to be effective for reducing depression in psychiatric patients [13]. This may actually be due to their effect for reducing fatigue, which is known to co-occur with depression, and/or it may be due to their effect for reducing body temperature, also known to be elevated in persons with depression (for comment, see [14]).

Compliance with ethical standards

Ethical standards This study was approved by the ethical review board of University Hospital San Raffaele, Milan. All participants provided written informed consent before enrollment.

Conflicts of interests VM Leavitt, E DeMeo, and G Riccitelli report no disclosures. MA Rocca received speaker honoraria from Biogen Idec, Sereno Symposia International Foundation, and Novartis and receives research support from the Italian Ministry of Health and Fondazione Italiana Sclerosi Multipla. G Comi has received consulting fees for participating in advisory boards from Novartis, Teva Pharmaceutical Industries Ltd, Sanofi-Aventis, Merck Seronon, Bayer Schering Pharma, Actelion Pharmaceuticals Ltd, and GeNeuro, and lecture fees from Novartis, Teva Pharmaceutical Industries Ltd, Sanofi-Aventis, Merck Seronon, Biogen-Dompe, Bayer Schering Pharma, and Serono Symposia International Foundation. M Filippi is Editor-in-Chief of the Journal of Neurology; serves on scientific advisory boards for Teva Pharmaceutical Industries Ltd.; and has

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