Brain temperature is elevated in relapsing-remitting relative to progressive multiple sclerosis

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TARGET AUDIENCE: Inflammation is a ubiquitous process leading to symptom worsening and disease progression in multiple sclerosis (MS)[1]. A central challenge in treating patients with relapsing-remitting MS (RRMS) is that 90% of disease-related inflammatory activity is 'clinically-silent,' that is, not accompanied by a clinically-evident relapse (i.e., symptom exacerbation)[2]. We recently reported elevated endogenous body temperature in RRMS patients relative to progressive MS patients in the absence of exogenous heat exposure[3], an observation never before reported despite the long-standing literature describing negative consequences of experimental and environmental heat exposure in MS patients (i.e., Uhthoff's phenomenon[4]). Elevated body temperature may result from clinically-silent brain inflammation in RRMS. If so, brain temperature should also be elevated in RRMS patients relative to progressive patients, for whom inflammation is less prevalent[6]. PURPOSE: To compare brain temperature between patients with RRMS and progressive courses of MS. Confirmation of our hypothesis that brain temperature is elevated in RRMS relative to progressive MS will support brain temperature as a biomarker of clinically-silent inflammation in RRMS. METHODS: We used MR spectroscopy to derive brain temperature in 14 patients (9 RRMS, 3 SPMS, 2 PPMS). The scans were done on a Siemens Skyra 3T scanner using a single voxel PRESS MRS sequence, with TE = 30 ms, spectral width = 1200 Hz, spectral points = 1024. Voxel was a 20x20x20 mm cube in right frontal cortex of each patient. The spectrum line-shape fitting was done using jMRUI software[7]. The position shift between water peak and NAA peak was used to estimate the temperature using the following equation[5]: $T_{brain} = 36 - [103.80 \times (\Delta_{H20-NAA} - 2.6759)]$. MRS permits non-invasive measurement of brain temperature based on the dependence of hydrogen bonding to temperature; measuring the shift in spectral position of the water signal relative to a reference metabolite (N-acetyl-aspartate) allowed for derivation of brain temperature with reported accuracy of ± 0.1°C[5]. RESULTS: Brain temperature was higher in RR than progressive patients (RRMS: 37.71°C ± 1.09, progressive: 36.92°C ± .93; absolute difference = 0.79 °C), as was body temperature measured aurally (RRMS: 36.98 ± .26, progressive: 36.59 ± .70), supporting our hypothesis that RRMS patients have higher brain temperature (likely due to brain inflammation) than progressive MS patients (consistent with previous reports of lesser brain inflammation in progressive courses of MS)[6]. In addition, brain temperature was correlated with body temperature (r=.475, p= 0.05). DISCUSSION: Elevated brain temperature in RRMS patients may indicate active inflammatory processes which can currently only be estimated through invasive Gadolinium-contrast enhancing MRI. Measuring brain temperature with MRS thermometry in RRMS will potentially allow for immediate treatment of clinically-silent disease activity, which is damaging to the brain. CONCLUSION: These findings provide preliminary support for body and brain temperature as biomarkers of clinically-silent brain inflammation in RRMS patients. The need for such biomarkers is critical, as the majority of active MS lesions are clinically silent, and therefore go undetected and untreated, leading to worse future disability.

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