Serial proton MR spectroscopy of gray and white matter in relapsing-remitting multiple sclerosis

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TARGET AUDIENCE: Neurologists, multiple sclerosis researchers

PURPOSE: To characterize and follow the global gray and white matter (GM/WM) metabolism in early relapsing-remitting multiple sclerosis (RR MS) using proton magnetic resonance spectroscopic imaging (^{1}H-MRSI).

PATIENTS AND METHODS: 29 patients (20 women) with clinically definite RR MS[1] for less than 6 years, were recruited prospectively to be scanned semi-annually for 3 years (7 scans each). 10 age- and gender-matched (8 women) healthy volunteers were to be scanned annually (4 scans each). *Post-hoc* exclusion criterion was <5 scans for patients and <4 for controls.

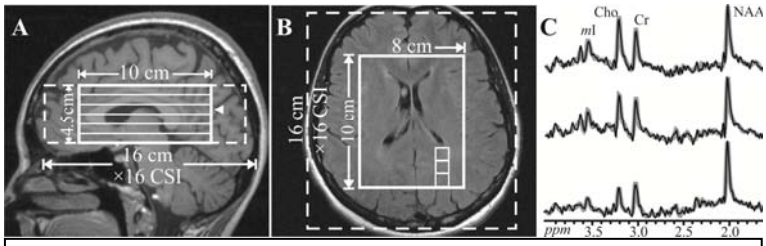

Fig. 1: Sagittal T_1-weighted (**A**) and axial FLAIR (**B**) MRI of a patient overlaid with the ^{1}H-MRSI VOI (solid white lines) and field-of-view (dashed lines). The location of **B** is indicated on **A** by an arrowhead. CSI=chemical shift imaging. (**C**) Real part of the ^{1}H spectra from the voxels indicated on (**B**), superimposed with their fitted model functions (gray lines).

Measurements were done at 3 T. MP-RAGE images were acquired for ^{1}H-MRSI volume-of-interest (VOI) guidance and for tissue segmentation. Axial T_2-weighted FLAIR images were acquired for lesion volumetry. The 10×8×4.5=360 cm^3 ^{1}H-MRSI VOI (*TE*/*TR*=35/1800 ms, 6 slices, 480 voxels, 0.75 cm^3 each) was image-guided over the corpus callosum, as shown in **Fig. 1A-B**. At two averages, the ^{1}H-MRSI took 34 minutes and the entire protocol less than an hour.

The cerebro-spinal fluid (CSF), GM and WM masks were co-registered with the ^{1}H-MRSI grid using in-house software. The VOI fractions: GM_f, WM_f, CSF_f were defined as the respective mask volume in all 480 voxels divided by the 360 cm^3 VOI volume. Absolute metabolite amounts of *N*-acetylasparte (NAA), creatine (Cr), choline (Cho) and *myo*-inositol (*m*I) were obtained using phantom replacement with correction for T_1 and T_2 relaxation time differences. Global GM and WM concentrations were calculated using linear regression as previously described[2]. Two-way analysis of variance was used to compare patients to controls in cross-sectional comparisons and random coefficients regression was used to model longitudinal changes. Linear regression was used to test for correlations between changes in metabolites and in CSF_f, GM_f, WM_f, lesion volume, Expanded Disability Status Scale (EDSS) scores and relapses.

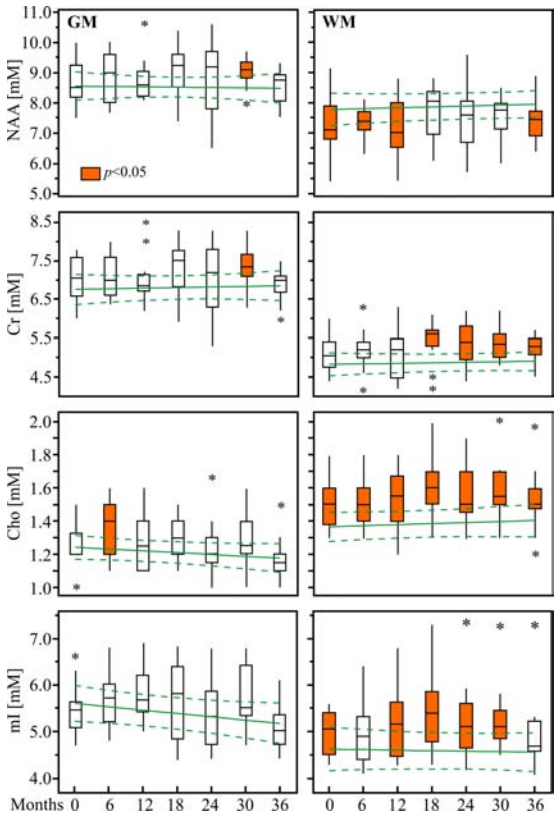

Fig. 2: Box plots of the patients GM and WM NAA, Cr, Cho and *m*I concentrations distributions, overlaid on the regression line of the corresponding average concentrations and 95% confidence intervals (dotted lines) of the controls. Orange fill: patients' distributions significantly different from the controls'.

RESULTS: 18 patients (13 women) and all controls met the enrollment criteria.

Cross-sectional: The average (over all time points) patients' WM Cr, Cho and *m*I concentrations were higher than the controls' (all $p \leq 0.01$). Patients' values were higher at all time points, by a range of 8-16% for Cr, 4-13% for Cho, and 7-17% for *m*I. The patients' WM NAA was lower with a trend on average ($p=0.07$), but statistically lower at 4/7 time points (**Fig. 2**, right panel). In GM, there were no differences in the average concentrations over all time points, but there were differences at single time points in 3 metabolites (**Fig. 2**, left panel). The patients' average CSF_f was higher than controls'. Patients' average VOI T_2 lesion load was 3.9±6.1 cm^3 (median: 2.1 cm^3).

Longitudinal: There were significant intra-cohort rates of change only for patients: (*i*) increasing WM Cr, Cho and NAA, decreasing GM Cho and *m*I (all $p \leq 0.05$); and (*ii*) increasing CSF_f and lesion volume and decreasing WM_f (all $p \leq 0.01$). There were no significantly different inter-cohort (patients' *versus* controls') rates of change, but there was a trend for different CSF_f rates ($p=0.06$). Finally, the rates of change in GM or WM metabolite levels did not correlate with the rates of change of CSF_f, GM_f, WM_f, lesion volume, EDSS or relapses, with no trends observed.

DISCUSSION AND CONCLUSION: To our knowledge, the data here represents the most frequent ^{1}H-MRS MS follow-up for the longest duration. In contrast to previous serial ^{1}H-MRS, this study: (*i*) assessed metabolism of a large brain volume; (*ii*) accounted for partial volume effects; and (*iii*) investigated diffuse involvement. We found that WM glial abnormalities were larger in magnitude than the axonal and increased over time independently of conventional clinical or imaging metrics and despite treatment. In contrast, the axonal abnormalities showed partial recovery, suggesting that patients' lower WM NAA levels represented a dysfunction, which may abate with treatment. Absence of widespread diffuse changes in GM suggests that injury there is minimal, focal, or heterogeneous between cortex and deep GM nuclei.

REFERENCES:

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