[1]H MRS Measures at Baseline Predict Cognition at 6 Months in Patients with Multiple Sclerosis

A. Tudorica[1], C. Christodoulou[2], L. Krupp[2], P. Roche[1], P. Melville[2], W. Scherl[2], W. MacAllister[2], W. Huang[3]

[1]Radiology, State university of New York, Stony Brook, NY, United States, [2]Neurology, State university of New York, Stony Brook, NY, United States, [3]Medical Physics, Memorial Sloan-Kettering Cancer Center, New York, NY, United States

Introduction Multiple sclerosis (MS) is the most common inflammatory demyelinating disease of the CNS, characterized by repeated cycles of white matter (WM) damage, recovery, and injury. [1]H MRS studies (1-4) of patients with MS have shown decreased N-acetylaspartate (NAA) levels in brain lesions and normal appearing WM (NAWM), which is related to the axonal damage or dysfunction. The decrease of NAA levels was found to be associated with cognitive deficits, as well as severity of atrophy in MS patients (5). In this study, neuropsychological tests were performed at baseline and 6 months later as part of a clinical trial to enhance cognitive functions with an acetylcholinesterase inhibitor (donepezil). [1]H MRS findings at baseline were correlated with the baseline and 6-month cognitive performances of the patients.

Methods 37 MS patients (7 male and 30 female; age range: 20-55 yrs, mean ± SD = 44 ± 8 yrs) were recruited for this study. They were clinically described as relapsing remitting (n = 22) and secondary progressive (n = 15) MS patients. They were evaluated at the baseline with the expanded disability status scale (EDSS) and the scores ranged from 0 to 6.5 with mean ± SD = 3.8 ± 1.9. Prior to the enrollment in the placebo/donepezil treatment study (baseline), and following the completion of the 6-month treatment, each MS patient underwent a modified version of the Brief Repeatable Battery (BRB) of neuropsychological tests for assessment of the cognitive functions. The BRB tasks are among those most sensitive to cognitive impairment in MS (6). Within the study population, 18 received placebo, while 19 received donepezil treatment.

MRI/MRS scanning sessions were performed at the baseline using a 1.5 T Philips (Marconi Edge) whole-body scanner with the body coil as the transmitter and a birdcage head coil as the receiver. Prior to MRS, routine volumetric T_1- and T_2-weighted, as well as multi-slice FLAIR images were acquired in the axial plane. Single slice multi-voxel [1]H MRS was performed with a PRESS sequence with TE = 135 ms, TR = 1500 ms, 16 cm FOV, 2D phase encoding (16x16), and 2 scan averages. Using FLAIR images as scouts, the MRSI slice with 2 cm thickness was taken through the posterior and anterior aspects of the corpus callosum (2). The total MRI/MRS scanning time was less than one hour.

Proton spectra from the left and right posterior periventricular (LPPV and RPPV) voxels were processed with 3 Hz line broadening, given the prevalence of lesions in periventricular tissue in MS (2). The periventricular voxels were selected through elimination of voxels with greater than 30% cerebral spinal fluid and by anatomical placement. A proton spectrum from a NAWM voxel was also processed. Resonance peaks of NAA, total creatine (Cr) and choline compounds (Cho) were identified and their peak area ratios were calculated.

Correlation analysis between metabolite ratios and cognitive functions was performed using partial correlations, controlling for age, education, and drug treatment effects.

Results The baseline values of LPPV and RPPV NAA/Cr and NAA/Cho ratios were found to be positively correlated with both the baseline and 6-month overall BRB scores, which provide composite measures of cognitive functions. The correlation coefficient and significance (r and P) values are listed in the Table. Figs. 1 and 2 show the examples of correlations between the baseline RPPV NAA/Cr, NAA/Cho ratios and baseline BRB scores in scatter plots. Similar correlations were also found between these metabolite ratios and the majority of the individual cognitive functions in the BRB tests. The correlations of NAA/Cr and NAA/Cho with BRB appeared stronger in the right hemisphere than the left. No significant relationship was found between NAA level and BRB in the NAWM voxel.

Table Partial Correlations between Cognitive and MRS Measures (N = 37)

	LPPV Baseline Metabolite Ratios		RPPV Baseline Metabolite Ratios	
	NAA/Cr	NAA/Cho	NAA/Cr	NAA/Cho
Baseline BRB	0.406 (P=0.017)*	0.366 (P=0.033)*	0.653 (P=0.000)*	0.587 (P=0.000)*
6-month BRB	0.393 (P=0.022)*	0.277 (P=0.113)	0.577 (P=0.000)*	0.547 (P=0.001)*

Partial correlations controlling for age, education, and drug treatment effects. *: statistically significant (P < 0.05).

Discussion The findings of positive correlations between baseline NAA/Cho, NAA/Cr and baseline, as well as 6-month cognitive functions in MS patients, suggest that [1]H MRS measurement of axonal damage or injury, implicated by decrease of NAA levels, not only provides the important neurochemical marker for cognitive impairment, but also may serve as valuable predictors of cognitive performance after 6 months. Thus, [1]H MRS examination may potentially play an important role in clinical management of MS patients. The exact reason for laterality of the relations between NAA levels and cognition is unclear. We have previously reported that cognitive impairment in MS patients is associated with the severity of central cerebral atrophy which can be extracted through segmentation of volumetric T_1- and T_2-weighted images (5). Separation of central cerebral atrophy into left- and right-hemisphere segments and examining its possible laterality in the future may help to elucidate the cause.

References 1. Gonen, O. *et al., Neurol.* **54**, 15 (2000). 2. Pan, J.W. *et al., Applied Neuropsychol.* **8**, 155 (2001). 3. Kapeller, P. *et al., J. Neurol.* **248**, 131 (2001). 4. De Stefano, N. *et al., Arch. Neurol.* **58**, 65 (2001). 5. Christodoulou, C. *et al., Neurol.* **60**, 1793 (2003). 6. Rao, S.M. *et al., Neurol.* **41**, 685 (1991).

Fig. 1

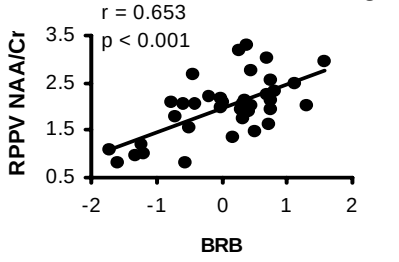

Fig. 2