Regional Brain Metabolite Changes and Their Correlations with Upper Motor Neuron Function Measures in ALS: Application of a Whole-brain Proton MRSI Method

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Introduction: Amyotrophic lateral sclerosis (ALS) is a devastating motor neuron disease affecting both lower and upper motor neurons (LMN and UMN), for which there is currently no reliable test available for assessment of UMN involvement. Recent studies also suggest that the disease affects non-motor brain regions [1, 2]. Availability of whole-brain MRS data will facilitate evaluation of metabolite alterations from any anatomical regions with no *a priori* hypothesis. Previous MRS studies using single-voxel and 2D-multivoxel methods have indicated potential for observing brain metabolite changes with ALS in a few selected anatomical regions. In this study, a volumetric spectroscopic data acquisition has been applied to ascertain brain metabolic changes in ALS and their correlation with UMN function measures. Regional analyses of data obtained from the corticospinal tracts (CST) are presented.

Methods: Thirteen definite-ALS patients and 11 age-matched controls were scanned on a 3T scanner using a 3D-MRSI sequence (135 mm slab, TR/TE=1710/70 ms, Tacq= 26 min.). Data were processed using the MIDAS software [3]. UMN functions were assessed using syllable repeat ('*la-la'* and '*pa-pa'* for tongue and lips, respectively) and finger and foot tap speed, each in 10 seconds [4]. Mean metabolite ratios of the ALS group (NAA/CR, CHO/CR and NAA/CHO), from ten regions-of-interest (ROI: medulla, pons, left and right internal capsule (IC), left and right corona radiata (CoR), left and right centrum semiovale (CS), and left and right precentral gyrus (PCG)) were calculated, then compared with that of controls; in addition, they were correlated with clinically-obtained UMN function measures. Two-tailed t-test and linear correlation were used, and a p-value of <0.05 was considered significant.

No	ROI	Ratio	Diff. (%)	p
1	CS–L	NAA/CR	-11.85	0.001
2	CS–R	NAA/CR	-14.66	0.0001
3	CoR–L	NAA/CR	-16.96	0.0001
4	CoR–R	NAA/CR	-11.89	0.0001
5	IC–L	NAA/CR	-13.80	0.002
6	IC–R	NAA/CR	-7.35	0.03
7	CS–R	NAA/CHO	-19.59	<0.01
8	IC–L	NAA/CHO	-19.16	0.02
9	IC–R	NAA/CHO	-12.80	0.05
10	Medulla	NAA/CHO	-13.82	0.04

Table 1: Metabolite ratios in 10 ROIs from patients with ALS that are significantly different from that of controls. Ratio difference in % and p-values were obtained by comparing data from ALS group with controls.

Results and Conclusion: In the ALS group, mean NAA/CR and NAA/CHO ratios significantly decreased in the 10 ROIs along the CST, starting from the centrum semiovale and moving inferiorly to medulla (see Table 1). Compared with data from the controls, the percentage of mean metabolite ratio reduction varied from ~7% for NAA/CR in the right-IC to ~20% for NAA/CHO in the right-CS.

Mean NAA/CR and NAA/CHO ratios from 6 anatomically different ROIs along the CST showed significant correlations with at least one of the UMN function measures. In Table 2 are shown a list of metabolite ratios that correlated with the UMN function measures together with their Pearson correlation coefficients (r-values) and p-values. Consistent positive correlations between NAA/CR or NAA/CHO and the UMN function measures, and a negative correlation between CHO/CR from the pons and *pa-pa* (a UMN measure) were observed. A representative regression plot between the left internal capsule NAA/CR and the right-finger taps (in 10 seconds) is shown in Figure 1. This plot indicates a strong association (r = 0.87) between an objective (NAA/CR) and a subjective measure (right finger tap in 10 s). The positive correlations between the metabolite ratios, NAA/CR and NAA/CHO, and UMN function measures suggest that either these metabolite ratios or their intensity- normalized values can be used as an objective marker for assessing UMN function.

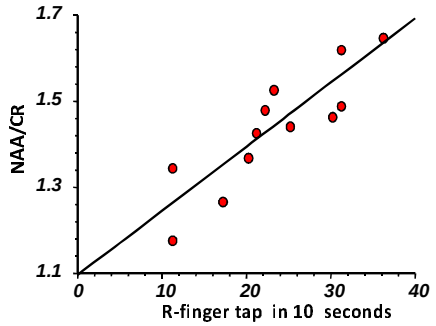

Figure 1: Regression plot between the left-internal capsule NAA/CR and right-finger tap in 10-seconds in the ALS group.

No	ROI	Met. Ratio	UMN Mea.	r	p
1	PCG-R	NAA/CR	*la-la*	0.67	0.01
2	PCG-R	NAA/CHO	*pa-pa*	0.61	<0.03
3	CS-L	NAA/CR	R-foot tap	0.63	0.02
4	CS-R	NAA/CR	*la-la*	0.77	<0.002
5	IC-L	NAA/CR	R-finger tap	0.87	0.0002
6	pons	NAA/CR	R-foot tap	0.64	0.02
7	pons	CHO/CR	*pa-pa*	-0.64	<0.03
8	pons	NAA/CHO	*pa-pa*	0.58	<0.05
9	pons	NAA/CHO	*la-la*	0.58	<0.05
10	Medulla	NAA/CR	*la-la*	0.73	0.01
11	Medulla	NAA/CR	R-foot tap	0.61	<0.05
12	Medulla	NAA/CHO	*pa-pa*	0.69	<0.02

Table 2: ROIs showing significant correlations between the mean metabolite ratios and UMN function measures in the ALS. In the ROI and UMN columns, R= right, L= left.

In summary, our findings are that: 1) mean metabolite ratios (specifically, NAA/CR and NAA/CHO) were significantly lower in ALS subjects compared to controls at multiple ROIs along the CST; and 2) mean metabolite ratios from six ROIs correlated with at least one of the clinical UMN function measures.

In conclusion, in this first whole-brain spectroscopic imaging study in ALS subjects it was found that the availability of whole-brain MRSI data greatly facilitated evaluation of metabolic changes in almost the whole-brain. The findings of decreased metabolic ratios in the CST and their correlations with UMN function measures suggest that NAA and CHO together may provide an objective biomarker for UMN dysfunction.

Acknowledgements: This work is supported by NIH grant, R01EB0822, and the Stanley Glaser Foundation of the University of Miami, and the Department of Radiology.

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