

Magnetic Resonance Spectroscopy of the Cervical Spine in ALS and Pre-symptomatic SOD1 Positive People

J. D. Carew^{1,2}, G. Nair³, S. Usher⁴, X. P. Hu³, and M. Benatar⁴

¹Carolinas HealthCare System, Charlotte, NC, United States, ²Biostatistics and Bioinformatics, Emory University, Atlanta, GA, ³Biomedical Engineering, Emory University, ⁴Neurology, Emory University

Purpose. We used MRS in the cervical cord of ALS patients, age-matched healthy controls, and pre-symptomatic SOD1 positive subjects to determine (a) if metabolite ratios differ in patients with ALS and whether or not they correlate with measures of disease severity, and (b) whether there are changes in metabolite ratios in asymptomatic SOD1 positive people in advance of the onset of disease.

Participants. We recruited 14 ALS patients (3 female, age 54 ± 12 years), 16 healthy controls (7 female, age 50 ± 13 years), and 7 pre-symptomatic SOD1 positive subjects (6 female, age 46.1 ± 12 years). Patients were clinically examined; the ALSFRS-R was administered, and FVC and finger/foot tapping speeds were measured. Control subjects were recruited to achieve approximate age matching with the ALS group.

Imaging Protocol. Volunteers were scanned on a 3T whole-body system with head, neck, and spine matrix coils. Imaging was performed with the two lower elements from the head coil, all channels from the neck coil, and the two upper elements from the spine coil. T2-weighted turbo spin echo localizer images were acquired in axial, coronal, and sagittal orientations to provide anatomical information for MRS voxel placement in the cervical spine. A rectangular VOI along the main axis of the cord with dimensions of (≈ 9 mm R-L) (≈ 7 mm A-P) (35 mm I-S) was positioned with the lower limit of the voxel approximately level with the inferior aspect of the C2 vertebral body (Figure 1). Voxel size in the A-P and R-L dimensions was maximized for each patient to cover the cross-section of the cord without extending beyond the confines of the cord. Presaturation bands were placed around the voxel to reduce outside signal contamination. Cervical spinal cord ¹H-MRS acquisitions were performed with a point-resolved spectroscopy (PRESS) spin-echo sequence with TR/TE = 2000/35 ms. A three-pulse chemical shift selective (CHESS) saturation sequence was used to suppress the water signal. A total of 256 signal accumulations were used for the water-suppressed spectra.

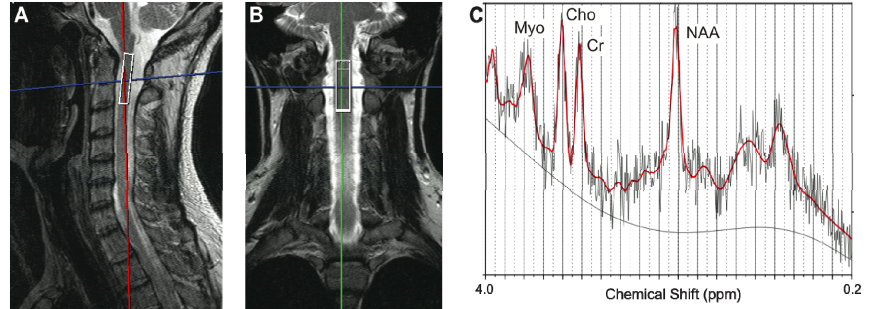


Figure 1: MRS voxels are placed to cover the spinal cord at the level of the C1-C2 vertebral body (A, B). The water-suppressed spectrum and LCModel fit (C) show good metabolic peak resolution for 256 signal accumulations.

MRS Data Processing and Statistical Analyses. The MRS data were fit with the LC model⁵⁵ using LCModel version 6.1-A (S.W. Provencher). Relative concentrations of choline (Cho), creatine (Cr), myo-inositol (Myo), and NAA were computed from estimates of metabolite peaks. Metabolite measurements were each normalized, separately, by Cho, Cr, and, in the case of NAA, Myo. Differences in metabolite ratios between ALS patients and controls were assessed with a two-tailed Wilcoxon rank-sum test. Among patients, correlations of metabolite ratios with clinical measures (ALSFRS-R and FVC) were assessed with Pearson correlation.

Results. We found metabolic changes in both the ALS and pre-symptomatic SOD1+ subjects, relative to healthy controls (Figure 2). We found significant correlations between FVC and both NAA/Cho and NAA/Myo (Figure 3).

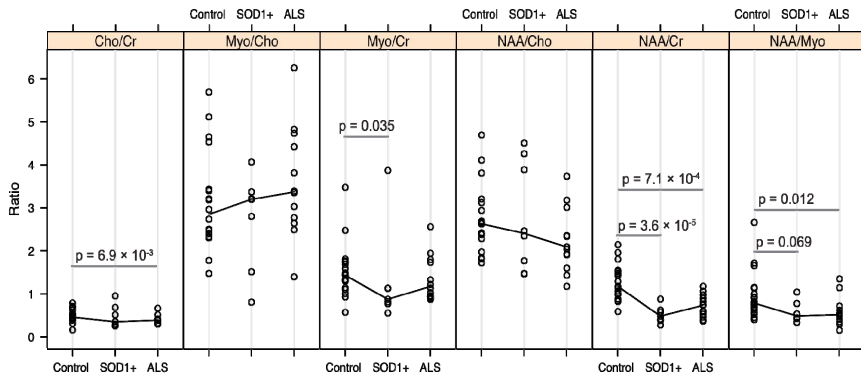


Figure 2: MRS metabolite ratios in the cervical cord from healthy controls, pre-symptomatic SOD1 positive subjects, and ALS patients. The line segments connect the group medians. Comparing ALS to controls, there are significant reductions in Cho/Cr (20%), NAA/Cr (40%), and NAA/Myo (38%). In SOD1+ subjects, relative to controls, there are significant decreases in Myo/Cr (14%), NAA/Cr (59%), and a nearly significant decrease in NAA/Myo (38%). No significant differences were found between SOD1+ subjects and ALS patients. The metabolic patterns of SOD1+ subjects fit between controls and ALS patients. Despite no clinical symptoms, SOD1+ subjects show significant metabolic differences from controls that are similar to ALS patients. This suggests that neurometabolic changes precede the onset of clinical symptoms. Statistical significance of differences was assessed with a Wilcoxon rank test of medians to mitigate outlier effects.

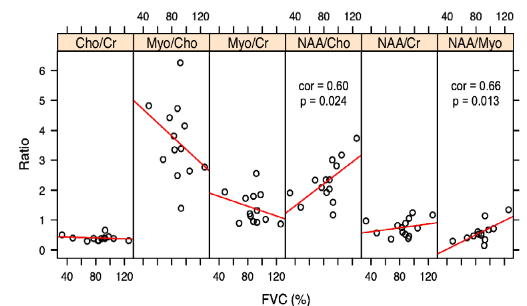


Figure 3: We found significant positive correlations of cervical spine measurements of NAA/Cho and NAA/Myo with forced vital capacity (FVC). The red line shows a linear fit to the data. Decreases in NAA reflect reduced neuronal function and correlate with worsening clinical function, as measured by FVC.

Conclusions.

Clear differences exist in cervical spinal cord metabolite ratios between patients with ALS and healthy controls. These changes in metabolite ratios in the cervical spinal cord correlate with cross-sectional measures of disease severity such as the percent predicted FVC. Changes in metabolite ratios in the cervical spinal cord are evident in asymptomatic SOD1 positive people in advance of the onset of symptoms or clinical signs of the disease.