High field MRS is more sensitive to progression of neurodegeneration than clinical decline in spinocerebellar ataxia type 1 (SCA1)

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Target audience: MR spectroscopists, neurologists, neuroscientists.

Introduction: Spinocerebellar ataxias (SCA) are hereditary movement disorders characterized by the degeneration of the cerebellum and brainstem1 with the most frequent forms being SCA1, SCA2, SCA3 and SCA6. High field proton MR spectroscopy (MRS) has revealed different neurochemical profiles between patients with SCA1 and healthy control subjects, specifically reduced total NAA (N-acetylaspartate + N-acetylaspartylglutamate, tNAA) and glutamate (Glu) and elevated myo-inositol (Ins) and total creatine levels in SCA1 relative to controls2. In addition, tNAA, Glu and Ins correlated with the clinical status of the patients cross-sectionally3. However, the sensitivity of these MRS markers to disease progression in patients has not been determined previously. The aim of this study was to assess the sensitivity of MRS, in comparison to clinical assessment, to detect longitudinal changes due to disease progression in SCA1.

Methods: Eleven early-moderate stage patients with SCA1 (genetically confirmed) and 10 healthy subjects were studied at baseline and after an ~18 month follow-up. The ataxia severity was assessed at each visit with the Scale for the Rating and Assessment of Ataxia (SARA) score, which yields a composite ataxia score in the range of 0 (no ataxia) – 40 (most severe ataxia)3. All MR measurements were carried out on a 3 T Siemens scanner using the standard body coil for excitation and 32-channel head coil for reception. A modified semi-LASER sequence4 ($T_E = 28$ ms, $T_R = 5$ s, 64 averages) was used to acquire spectra from the cerebellar vermis, cerebellar hemisphere andpons. Spectra were processed in Matlab and quantified with LCModel5 with water scaling option using simulated basis spectra with a measured macromolecule spectrum. Only metabolites that were reliably quantified (Cramér-Rao lower bounds, CRLB $\leq 50\%$ and correlation $r > -0.5$) from at least half of the spectra from a particular brain region were included in the final analysis. Metabolite concentrations were determined after correcting for $T_2$ relaxation times, tissue water content and CSF contributions (determined using the fully relaxed unsuppressed water signals acquired at different $T_E$) in the selected VOI.

Results and Discussion: A significant reduction in [tNAA]/[Ins] was observed in the pons ($P=0.03$, Figure 1) in SCA1 at visit #2 vs. visit #1 while no difference was detected in controls ($P=0.46$) or the other two regions studied in both groups. This observation is consistent with a recent longitudinal MRI study6 that showed that the pontine volume was most sensitive to change among all brain regions investigated after a 2-year follow-up in a large SCA1 cohort. The pontine [tNAA]/[Ins] ratio was further found to be correlated with the clinical SARA score in SCA1 (Figure 2) at both visits. On the other hand, the change in the SCA1 SARA score between visits #1 and #2 was very small (mean change of 0.8 points) and did not reach statistical significance ($P=0.09$, paired, one-tailed t-test) suggesting that MRS was more sensitive to detect a small change due to disease progression. Note that two out of the 11 patients did not have any symptoms (based on their SARA scores of $\leq 1$). One of the two pre-symptomatic patients is clearly visible on both Figures where the metabolite ratio lies amongst the controls while the other one already shows neurochemical changes and is grouped with patients (Figures 1 and 2).

Conclusion: The present study shows that optimized MRS methodology, as implemented on a widely available clinical 3 T platform, is more sensitive to onset and progression of neurodegeneration than clinical assessment, indicating that the method can provide substantial benefits in reducing sample sizes in clinical studies and treatment trials for neurodegenerative diseases.


Supported by NIH grants R01 NS070815, P41 RR008079, P41 EB015894 and P30 NS076408.