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 brainstem[1] 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 controls[2]. In addition, tNAA, Glu and Ins correlated with the clinical status of the patients cross-sectionally[2]. 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 sequence[4] (T_E = 28 ms, T_R = 5 s, 64 averages) was used to acquire spectra from the cerebellar vermis, cerebellar hemisphere and pons. Spectra were processed in Matlab and quantified with LCModel[5] with water scaling option using simulated basis spectra with a measured macromolecule spectrum. Only metabolites that were reliably quantified (Cramér-Rao lower bounds, CRLB ≤ 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_Es) in the selected VOI.

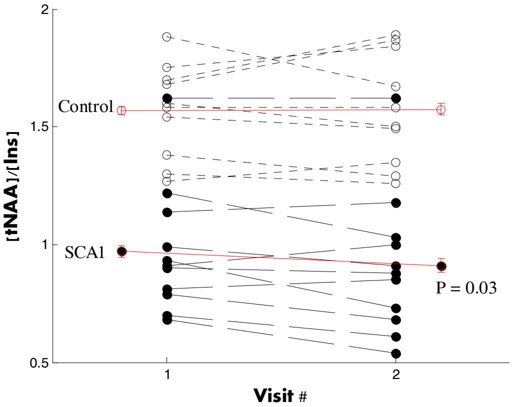

Figure 1: Longitudinal change of [tNAA]/[Ins] in the pons for SCA1 and control subjects. Mean change was tested per group with a paired one-tailed t-test. Error bars represent SEM.

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 study[6] 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 ≤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).

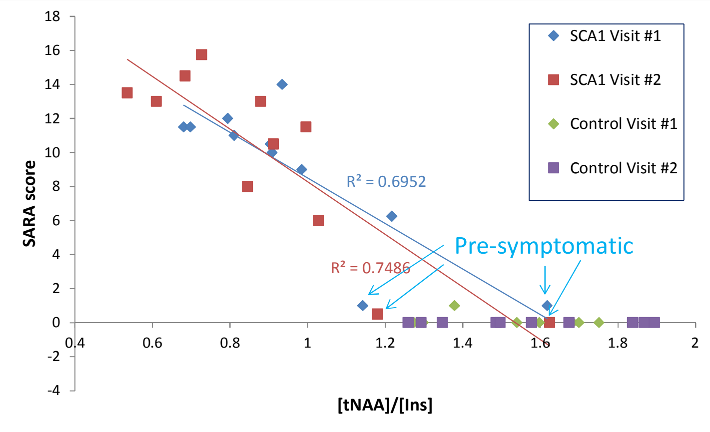

Figure 2: Relationship between [tNAA]/[Ins] and SARA score at baseline and at follow-up in SCA1 and control subjects. The arrows show 2 patients without symptoms of ataxia.

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.

References: 1. Taroni & DiDonato Nat Rev Neurosci 2004; 2. Oz et al. Mov Disord 2010; 3.Schmitz-Hübsch T et al. Neurology 2006; 4. Oz & Tkac MRM 2011; 5. Provencher MRM 1993; 6. Reetz et al Brain 2013.

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