Detection of Early Neurochemical Changes related to Neurodegeneration in a Spinocerebellar Ataxia Type 1 (SCA1) Mouse Model by \(^1\)H MRS at 9.4 Tesla

U. E. Emir\(^1\), H. B. Clark\(^1\), M. Vollmers\(^1\), D. M. Koski\(^1\), L. E. Eberly\(^1\), H. T. Orr\(^1\), H. Y. Zoghbi\(^2\), and G. Oz\(^1\)

\(^1\)University of Minnesota, Minneapolis, MN, United States, \(^2\)Baylor College of Medicine, Houston, TX, United States

Introduction
Hereditary spinocerebellar ataxias (SCAs) are a clinically and genetically heterogeneous group of neurodegenerative diseases characterized by loss of cerebellar Purkinje cells (PC) (1). The sensitivity of MRS biomarkers (NAA, glutamate, myo-inositol) to progressive neurodegeneration was previously reported in a transgenic mouse model of SCA1 (2). In that model, neuronal dysfunction apparent as dendritic atrophy started at 6 weeks and neurodegeneration progressed to severe pathology by one year. In order to identify MRS biomarkers of even earlier pathology, here we utilized a knockin mouse model of SCA1: The Sca\(^{154Q/2Q}\) line has a 154 polyglutamine repeat in the endogenous ataxin-1 protein (3) and presents with milder cerebellar pathology than the transgenic SCA1 mice studied before. We hypothesized that MRS biomarkers would be sensitive to disease even prior to the development of clear pathological changes and compared cerebellar neurochemical profiles of Sca\(^{154Q/2Q}\) mice longitudinally to those of wild type (WT) littermates to test this hypothesis.

Methods
Two groups of mice (Sca\(^{154Q/2Q}\) knockin mice, N=10, and WT littermates, N = 9) were scanned at 9.4 tesla under 1.5 - 2% isoflurane anesthesia at ages 6, 12, 24 and 39 weeks with a quadrature surface coil. Spectra from the cerebellum (5 - 7 \(\mu\)L volumes) were acquired with a short-echo (TE = 15 ms) LASER sequence (4). Metabolites were quantified with LCModel (5) using unsuppressed water as reference. The LCModel basis set was generated with the MATLAB software by simulating the spectral pattern of each metabolite using density matrix simulations (6). Only results with Cramér-Rao lower bounds (CRLB) \(\leq\) 50% were included in the analysis. A subset of the animals at each age was evaluated by histology performed on paraffin-embedded sections using hematoxylin-and-eosin and calbindin. Sca\(^{154Q/2Q}\) were compared to WT at each age using the two-tailed student’s t-test.

Results and Discussion
High spectral quality (Fig. 1) enabled reliable quantification of 18 metabolites. Four MRS biomarkers of early cerebellar neurodegeneration (taurine, total choline (tCho), glutamine and total creatine (tCr)) were identified (Fig. 2). Taurine was significantly lower in Sca\(^{154Q/2Q}\) mice than controls at all ages. tCho was lower and glutamine higher for Sca\(^{154Q/2Q}\) mice starting at 12 weeks, whereas tCr showed a trend to increase at 12 weeks, which became significant at 39 weeks. Taurine vs. tCho levels distinguished the Sca\(^{154Q/2Q}\) mice from controls starting at 12 weeks (Fig. 3). Taurine changes may represent osmolytic changes while increased glutamine and creatine may mark glial hypertrophy/hyperplasia. Although trends were observed for the neuronal markers NAA and glutamate to decrease in the Sca\(^{154Q/2Q}\) mice relative to WT, cerebellar disease did not reach a severe enough stage to reveal statistically significant differences in these. The Sca\(^{154Q/2Q}\) mice displayed very mild cerebellar pathology even at 39 weeks, restricted to heterotopic PCs, vacuoles in PCs and molecular layer thinning largely confined to the posterior lobules that were not included in the MRS voxel. Therefore, this study demonstrated that the MRS biomarkers are sensitive to very early changes related to neurodegeneration prior to overt pathology.

References:

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