Longitudinal Assessment of Neurodegeneration in a Spinocerebellar Ataxia Type 1 (SCA1) Mouse Model by ^{1}H MRS at 9.4 Tesla: Correlation with Histopathology

G. Oz[1], H. B. Clark[1], C. D. Nelson[1], D. M. Koski[1], P-G. Henry[1], M. Marjanska[1], D. K. Deelchand[1], and H. T. Orr[1]

[1]University of Minnesota, Minneapolis, MN, United States

Introduction

Hereditary spinocerebellar ataxias (SCAs) are a clinically and genetically heterogeneous group of neurodegenerative diseases characterized by loss of cerebellar Purkinje cells (1). As genetic neurodegenerative diseases they present the ideal test case to evaluate the potential of high field MRS to quantify biochemical and cellular events underlying and accompanying neurodegeneration. Here we utilized a transgenic mouse model (the *SCA1*[*82Q*] line) that overexpresses the mutant human ataxin-1 protein with an 82 glutamine stretch (82Q) in Purkinje cells (2). This model reproduces the cerebellar cortical pathology of the human disease and develops progressive ataxia and incoordination similar to the human phenotype. We hypothesized that MRS biomarkers would be sensitive to disease onset and progression, even prior to the development of clear pathological changes and the development of ataxia. We compared cerebellar neurochemical profiles of *SCA1*[*82Q*] mice to those of two control groups: *SCA1*[*30Q*] transgenic mice that overexpress the normal human ataxin-1 (2) and wild type mice (background strain FVB). To identify the neurochemical correlates of pathology, we further assessed a subset of the animals by histology.

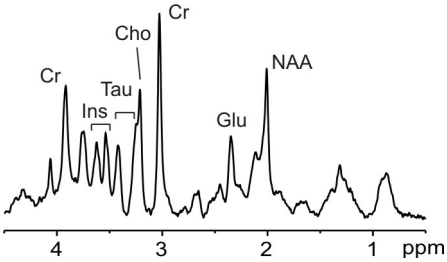

Fig. 1. ^{1}H MRS spectrum from an SCA1[82Q] mouse at 6 weeks of age.

Methods and Subjects

Three groups of male mice (*SCA1*[*82Q*] and the 2 control groups, N = 8 - 14 in each group) were scanned at 9.4 tesla under 1.5 - 2% isoflurane anesthesia at ages 6, 12 and 24 weeks with a quadrature surface coil. Spectra from the cerebellum (5 - 7 µL volumes) were acquired with a short-echo (TE = 15 ms) localization by adiabatic selective refocusing (LASER) sequence (3). Metabolites were quantified with LCModel (4) 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 (5). Only results with Cramér-Rao lower bounds (CRLB) ≤ 50% were included in the analysis. Metabolites quantified with CRLB ≤ 50% in at least half of the spectra were included in the neurochemical profile. The histology was performed on paraffin-embedded sections using hematoxylin-and-eosin and Luxol-fast-blue-PAS. Data from the different mouse groups were compared using the two-tailed student's t-test.

Results and Discussion

High spectral quality (Fig. 1) enabled reliable quantification of 18 metabolites in the mouse cerebellum. Six MRS biomarkers were identified, 4 of them (decreased NAA, taurine, increased *myo*-inositol, glucose) were significantly different in the *SCA1*[*82Q*] mice relative to controls at all ages, glutamate was lower at 12 and 24 weeks, and total creatine higher at 6 weeks (Figs. 2, 3). The *SCA1*[*82Q*] mice were distinguished from controls at each age without overlap in 2D plots of these biomarkers (Fig. 3). NAA and glutamate changes were likely indicative of loss of neuronal function and integrity. NAA levels were further correlated significantly with the molecular layer thickness (Fig. 4). Taurine changes may represent osmolytic changes as vacuoles are a prominent feature of the histopathology in these mice. Increased *myo*-inositol is likely a marker of glial hypertrophy/hyperplasia and increased glucose levels indicative of decreased glucose utilization. The clear separation of the *SCA1*[*82Q*] mice from controls already at 6 weeks demonstrates the ability of high field MRS to detect pre-clinical disease, as these animals only display a very mild neurological deficit (6) with minimal pathological correlates at this age.

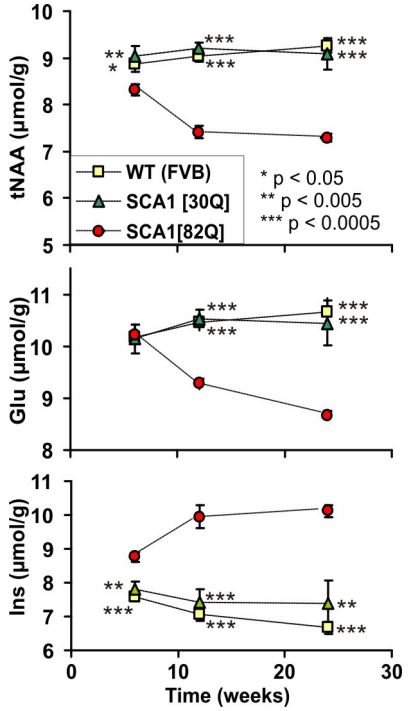

Fig. 2. Progression of select neurochemical alterations with disease. Error bars represent SEM. Statistical comparisons are FVB vs. SCA1[82Q] and SCA1[30Q] vs. SCA1[82Q].

References: 1. Taroni F & DiDonato S, *Nat Rev Neurosci*, 5: 641, 2004. **2.** Burright et al, *Cell*, 82: 937, 1995. **3.** Garwood & DelaBarre, *J Magn Reson*, 153: 155, 2001. **4.** Provencher SW, *MRM*, 30: 672, 1993. **5.** Henry et al, *MRM*, 55: 250, 2006. **6.** Clark et al, *J Neurosci*, 17: 7385, 1997.

Supported by NIH R21 NS060253, P41 RR08079, P30 NS057091, Keck Foundation and Bob Allison Ataxia Research Center.

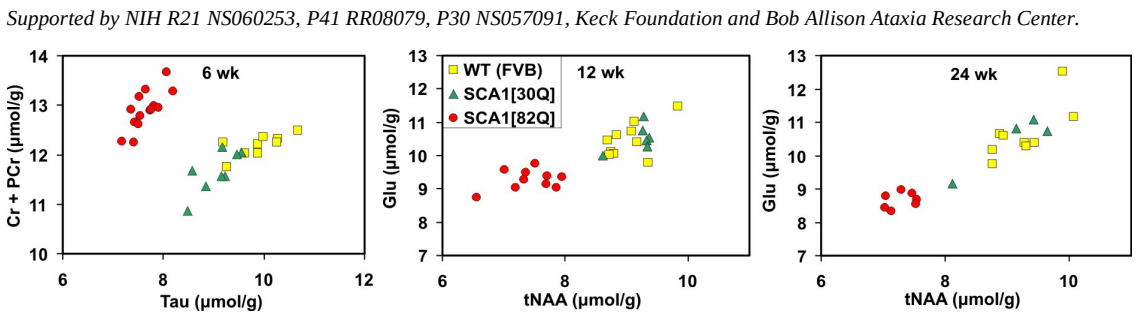

Fig. 3. Metabolite concentrations of individual mice at 3 different ages. Cr: creatine, PCr: phosphocreatine; Tau: taurine; Glu: glutamate, tNAA: N-acetylaspartate + N-acetylaspartylglutamate.

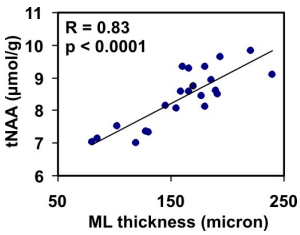

Fig. 4. Correlation of NAA with the primary fissure molecular layer thickness. Data from all groups combined.