7T MRS Classification of Clinically Similar Ataxias (SCA1, SCA2, SCA3 and SCA6)

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Introduction

Hereditary spinocerebellar ataxias (SCAs) are movement disorders characterized by neurodegeneration in the cerebellum and in many cases in the brainstem (1). The most common forms, SCA1, SCA2, SCA3 and SCA6, all polyglutamine disorders, display substantial overlap in clinical presentation and conventional MRI (2). A prior MRS study suggested that neurochemical alterations can be utilized to differentiate SCA types (3). Running the full profile of available genetic tests for ataxias is expensive and identifying objective imaging markers that can differentiate SCAs can help guide genetic testing in the absence of family history. Reduced NAA levels are considered a non-specific MRS change common to all neurodegenerative diseases. SCAs also present the ideal test case to investigate if the pattern of neurochemical alterations differs between neurodegenerative diseases that affect the same brain region and are therefore clinically similar. Here we investigated if neurochemical levels measured by ultra-high field MRS can distinguish different SCA subtypes with overlapping clinical presentation as assessed by the standardized Scale for the Assessment and Rating of Ataxia(SARA)(4).

Methods

The ataxia type of all patients was genetically confirmed. Sixteen patients with SCA1 (age 51 ± 11 (SD) years, SARA, 9 ± 4), 5 patients with SCA2 (37 ± 11 years, SARA, 9 ± 5), 5 patients with SCA3 (54 ± 13 years, SARA, 8 ± 3), 8 patients with SCA6 (65 ± 9 years, SARA, 11 ± 8) and 22 healthy volunteers (55 ± 15 years, SARA, 0.1 ± 0.2) were studied. Measurements were performed on a 7T scanner (Siemens). A 16-channel transceiver array coil (5) and B_1^+ phase shimming (6) were used. Spectra were acquired from the vermis (10 x 25 x 25 mm^3), cerebellar hemisphere (17 x 17 x17 mm^3) and pons (16 x 16 x 16 mm^3) using a semi-LASER sequence (TR=5s, TE= 26ms, NEX=64) (7). Metabolites were quantified with LCModel (8) using the unsuppressed water signal as reference. Only those measured reliably (Cramér-Rao lower bounds (CRLB) < 50%, cross correlation coefficients r > -0.5) from more than half of the spectra were used in the analysis. Concentrations were corrected for the amount of CSF present in each VOI.

Results and Discussion

Spectra with good SNR and spectral resolution were consistently obtained from all groups (Fig. 1). The patterns of neurochemical alterations differed between ataxia types. For instance, lack of pontine involvement in SCA6 distinguished this group from the other SCAs (Fig. 1), consistent with known pathology (1, 2). SCA2 was characterized with more extensive changes in tNAA and *myo*-Ins in the pons than SCA1 and SCA3 (Fig. 1). Finally, higher tCho levels in the vermis in SCA1 than SCA3 were apparent. These MRS predictors were used for a tree classification procedure (Fig. 2) and lead to 88% accurate classification of all subjects. Fig. 3 demonstrates the clustering, based on 2 neurochemicals only, of SCA1, SCA2 and SCA3, groups which showed complete overlap in SARA scores (Fig. 4) and which have been challenging to discriminate using MRI. This study demonstrates the potential for MRS to classify neurodegenerative diseases with overlapping clinical presentation.

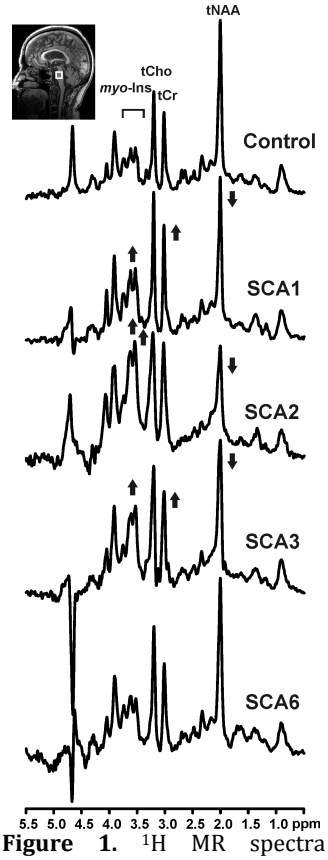

Figure 1. ^{1}H MR spectra obtained at 7T with semi-LASER from the pons in five representative participants.

References: **1.** Taroni F & DiDonato S, *Nat Rev Neurosci*, 5: 641, 2004; **2.** Schols L et al., *Lancet Neurol*, 5:291, 2004; **3.** Oz et al. *Cerebellum*, 10:208, 2011 ; **4.** Schmitz-Hübsch T et al., *Neurology*, 66 :1717, 2006 ; **5.** Adriany et al. *MRM*, 59:590, 2008 ; **6.** Metzger et al. *MRM*, 59:396, 2008 ; **7.** Oz & Tkac *MRM*, 65:901, 2011 ; **8.** Provencher SW, *MRM*, 30:672, 1993. *Supported by NIH R01 NS070815, P41 EB015894, P30 NS057091, P30 NS076408, S10 RR026783, WM KECK Foundation.*

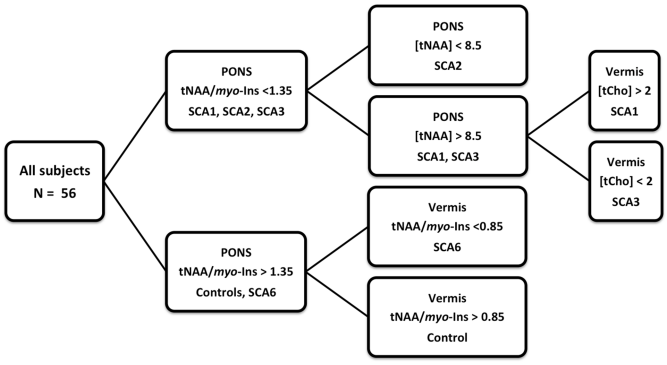

Figure 2. Tree classification procedure. The MRS predictors and the threshold levels used (no units for ratios, µmol/g for concentrations) are shown at each step. Only 7 of 56 subjects were misclassified.

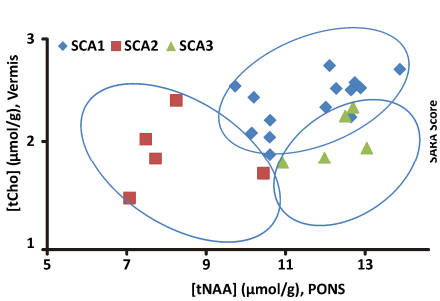

Figure 3. Classification of SCA1, SCA2 and SCA3 by MRS.

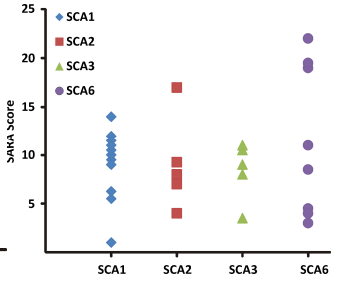

Figure 4. SARA scores. Highest disability is indicated by a SARA score of 40.