Quantitation of Cellular and Biochemical Alterations in Hereditary Ataxias by 1H MRS at 4 Tesla

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Introduction

Hereditary spinocerebellar ataxias (SCAs) are a clinically and genetically heterogeneous group of neurodegenerative diseases characterized by loss of cerebellar Purkinje cells in combination with neuronal loss in other regions, such as the pons (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, such as gliosis, inflammation and oxidative stress. As such, diagnostic certainty provided by genetic testing eliminates the possibility of including a heterogeneous study sample with diverse tissue biochemistry. Most MRS studies of ataxias to date reported differences in ratios of NAA, creatine and choline-containing compounds between patients and controls (2). The aim of the current study was to determine what biochemical and cellular changes can be measured reliably at 4 T in cerebellar neurochemical profiles of patients with two prototypic ataxias, namely SCA2, a cerebellar-predominant multiple system atrophy and SCA6, a pure cerebellar ataxia.

Methods and Subjects

Ten healthy volunteers (5 M/5 F, average age±SD: 32±12 years), 4 patients with SCA2 (3 M/1 F, 54±5 years) and 4 patients with SCA6 (1 M/3 F, 54±9 years) participated in the study. A 4 Tesla / 90 cm magnet (Oxford/Varian) and a TEM volume coil (3) were utilized. Spectra from vermis ($1\times2.5\times2.5$ cm^3), cerebellar hemispheres ($1.7\times1.7\times1.7$ cm^3, in white matter) and pons ($1.6\times1.6\times1.6$ cm^3) were acquired with STEAM combined with OVS and VAPOR water suppression (4) (TE=5ms, TM=42ms, TR=4.5s, NEX=128). First- and second-order shims were adjusted with FASTMAP with echo-planar readout (5). Metabolites were quantified with LCModel (6) using unsuppressed water as reference. 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. Due to significant atrophy in patients, all concentrations were corrected for the amount of CSF present in each VOI.

Results and Discussion

High spectral quality (S/N and resolution) was achieved enabling detection of metabolite alterations in individual patients (Fig. 1). Nine-to-twelve metabolites were quantified reliably in the 3 VOI (Fig. 2). No indication for age-dependent changes in metabolite levels was present based on two age-matched (52 and 53 years old) control participants, allowing the comparison of patients to the young control group.

Major alterations were detected in all 3 areas (Fig. 2). Notably, gliosis (increased Gln & Ins) was indicated both in SCA6 and SCA2, while neuron loss (decreased NAA & Glu) was only significant in SCA2 in the remaining vermis tissue. Cr and Glc + Tau were also increased in the same area, which may result from gliosis and reduced glucose utilization, respectively. Involvement of cerebellar white matter was more pronounced in SCA2 than SCA6, while involvement of pons was restricted to SCA2 as expected from known pathology. In conclusion, ^{1}H MRS at 4T can be used to non-invasively evaluate disease- and region- specific cellular and biochemical events in neurodegenerative diseases with high accuracy and precision.

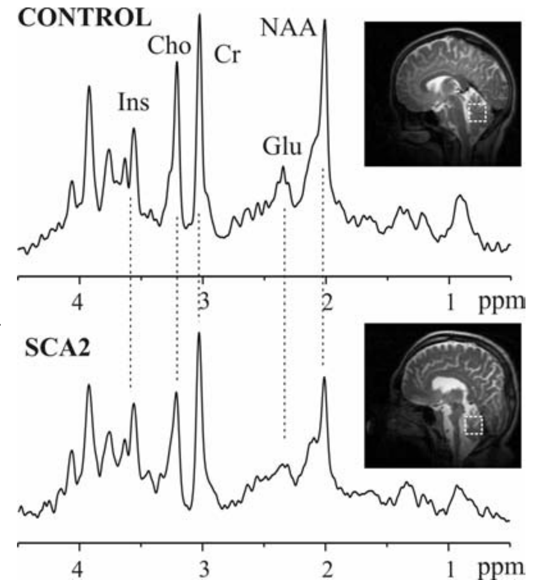

Fig. 1. Spectral changes in the vermis of a patient with SCA2 relative to a healthy volunteer. Changes in *myo*-inositol (Ins), choline (Cho), creatine (Cr), glutamate (Glu), N-acetylaspartate (NAA) are indicated. Voxels (6.3 ml) shown on T_2-weighted images.

References

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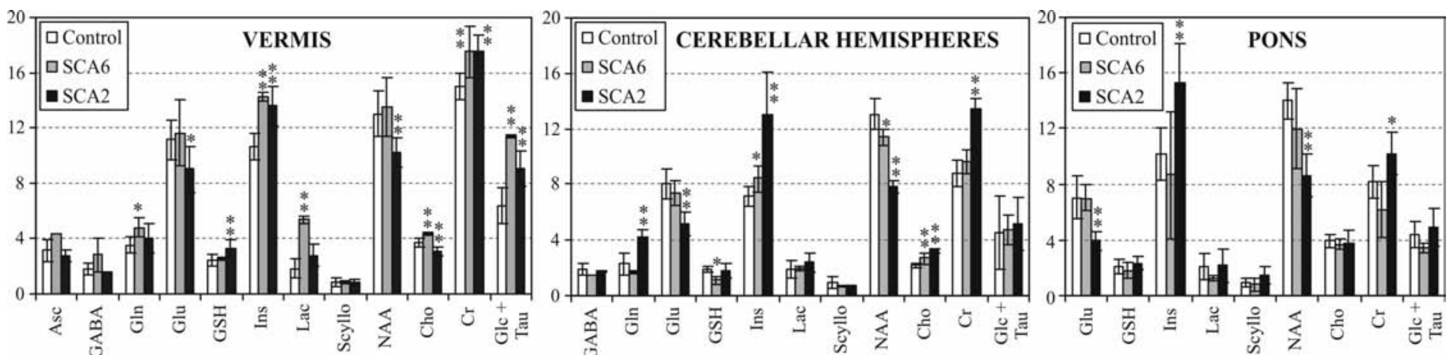

Fig. 2. Average (± SD), atrophy corrected metabolite concentrations (μmol/g) in vermis, cerebellar hemispheres and pons of controls (N=10 for vermis, N=6 for cerebellar hemispheres and pons) and patients with SCA6 (N=4) and SCA2 (N=4). Asc: Ascorbate, GABA: γ-aminobutyric acid, Gln: glutamine, Glu: glutamate, GSH: glutathione, Ins: *myo*-inositol, Lac: lactate, Scyllo: *scyllo*-inositol, NAA: N-acetylaspartate + N-acetylaspartylglutamate, Cho: choline-containing compounds, Cr: creatine + phosphocreatine, Glc: glucose, Tau: taurine. *: $p < 0.05$, **: $p < 0.01$ between patient and control groups.