Proton Spectroscopy of the Motor Pathway in Patients with Spinocerebellar Ataxia (SCA).

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Introduction

The spinocerebellar ataxias (SCA) are a heterogeneous group of autosomal dominant ataxias characterised by neurodegeneration of the brainstem nuclei, the cerebellar pathways and spinal cord. This group of ataxias continues to expand, but they are generally related to a trinucleotide repeat (CAG) encoding for polyglutamines and affecting different genetic loci[1]. It is clear that within the definition of SCA, the various genetic defects lead to a wide range of pathological states throughout the CNS. MR imaging and spectroscopy offer the only non-invasive approach to investigate the relationship between structure, metabolism and clinical function in these patients. Prior studies have used proton MRS to investigate the brainstem and cerebellum in patients diagnosed as SCA1, 2 and 6[2,3,4]. In this current study, we extend these observations along the motor pathway, by examining voxels in the parietal lobe, brainstem, cerebellum and spinal cord and relate these observations to clinical function.

Methods

Patients: Twelve patients with spinocerebellar ataxia (mean age 53±12 years, 8 female) were investigated and compared with 13 healthy controls (mean age 37±12 years, 4 female). Clinical assessment included neurological examination, the International Cooperative Ataxia Rating Scale (ICARS) and disease duration. Patients had previously been confirmed to have the CAG repeat mutations in SCA1 (n=4), SCA2 (n=1), SCA3 (n=1) or SCA6 (n=6) genes. All investigations were approved by the local ethical review committee.

MR Protocol: Subjects were studied in a 2T whole body spectrometer with a Bruker Avance console (Bruker Medical GmbH, Ettlingen, Germany) and a birdcage headcoil. Following transverse T2 weighted imaging (TSE sequence, TR=3s, TE=80ms, 20×5mm thick contiguous slices), single voxel proton spectra (PRESS localised, TR=3s, TE=30ms, 128 averages) were acquired from a voxel in normal appearing fronto-parietal white matter (2.2×2.2×2.0 cm^3), a voxel in the cerebellum (2.2×2.2×2.0 cm^3), and a voxel in the brainstem (1.3×1.0×4.0 cm^3). Subjects were then removed from the magnet and the coil exchanged for a purpose-built quadrature surface coil designed for use in the cervical spinal cord. Subjects were repositioned in the magnet and following sagittal and transverse T1 weighted imaging of the spinal cord, a proton spectrum was collected from a 9×7×35mm^3 voxel located at the level of C3 according to our previous protocol[5] (cardiac gated PRESS sequence, TR=3s, TE=30ms, 256 averages). Due to the long protocol (1.5 hours) and technical challenges associated with spinal MRS, successful spectra were collected from the cord of 8 patients (3 SCA1, 1 SCA2, 4 SCA6). In all four MRS voxels, water data were collected for absolute quantitation using a fully relaxed (TR=10s) multi-echo sequence with echo times varying from 35 to 2235 ms.

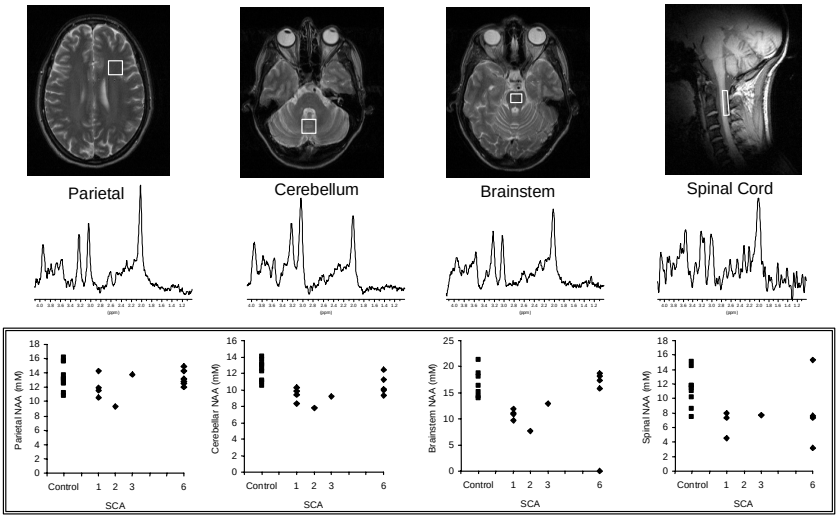
Data Processing: Spinal cord images were used to determine cross sectional area of the cervical cord at the level of C3. Proton spectra were analysed using an LCmodel[6] style analysis and quantified in absolute terms against total tissue water determined by biexponential analysis of the multi-echo water spectra. Statistical analysis was performed in SPSS 11.0 (SPSS Inc. Chicago, USA) using Students t-test.

Results

The location of each voxel and typical spectra in a SCA patient (SCA1) are illustrated in figure 1. As a group, metabolic abnormalities were only observed in the concentration of NAA. All other metabolites, in all voxels were not significantly different to control values. In fronto-parietal white matter [NAA] was not different from control values. However [NAA] was significantly reduced in the cerebellar voxel (9.8 ± 1.3 mM vs 12.3 ± 1.3 mM, $p<0.001$), brainstem voxel (12.2 ± 5.5 vs. 16.8 ± 2.7 mM, $p<0.05$) and spinal cord voxel (7.6 ± 3.4 vs 11.3 ± 2.5 mM, $p<0.03$). Sub-group analysis (although limited in number) showed a marked difference between SCA types (see figure 2). In the cerebellum, patients with SCA1, SCA2 and SCA3 all had [NAA] outside of the control range, while only 2 of the SCA6 patients were outside of control values. Similarly in the brainstem, patients with SCA1, SCA2 and SCA3 all had [NAA] outside of the control range, while all SCA6 patients were within control values. Spinal cord concentration of NAA (although having a larger spread of values due to signal to noise considerations) were decreased in 7 out of the 8 successful studies. There was no correlation between [NAA] and ICARS score in any voxel.

Discussion

Proton spectroscopy revealed marked regional differences between the axonal damage seen in patients with SCA6 and the remaining patients (SCA1, 2 and 3). As expected, the fronto-parietal white matter voxel (although placed within the main tracts passing into the brainstem and spinal cord), did not show any metabolic differences compared to control subjects. Cerebellar and brainstem changes were related to genotype with SCA6 patients having well preserved to normal levels of [NAA], whereas NAA was significantly reduced in the remaining patients. Our observations in the cerebellum support previous observations by MRS which reported reduced NAA/Cr ratio in the cerebellum of SCA2 compared to SCA6[3] and also in SCA1[3, 4].



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