Assessment of Oxidative Stress and Neuronal Viability in Friedreich's Ataxia by ^{1}H MRS at 4 Tesla

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Introduction

Friedreich's ataxia (FRDA) is the most common hereditary ataxia, with a typical onset around puberty (1). An autosomal recessive mutation results in reduced levels of frataxin protein and progressive loss of neurons in the spinal cord, dorsal root ganglia and cerebellum. Mitochondrial iron accumulation and protein, lipid and nucleic acid oxidation appear prominent in disease pathogenesis (1). So far, however, assessment of oxidative stress in this neurodegenerative condition has been limited to peripheral measurements. For example, alterations in the homeostasis of glutathione, a potent antioxidant, have been found in blood and fibroblasts of patients (2). We hypothesized that glutathione levels may also be altered in affected brain regions in FRDA. To determine if glutathione, as well as other markers of neuronal viability, are altered in FRDA, we compared the MRS neurochemical profiles of cerebella and pons of patients with FRDA to those of healthy controls.

Methods and Subjects

Twelve healthy volunteers (6 M / 6 F, mean age ± SD: 28 ± 7 years) and 5 patients with FRDA (2 M / 3 F, 25 ± 12 years) participated in the study. A 4 Tesla / 90 cm magnet (Oxford/Varian) and a TEM volume coil were utilized. Spectra from vermis (1 × 2.5 × 2.5 cm^3), cerebellar hemispheres (1.7 × 1.7 × 1.7 cm^3) and pons (1.6 × 1.6 × 1.6 cm^3) were acquired with STEAM as described previously (3) (TE = 5 ms, TM = 42 ms, TR = 4.5 s, NEX = 128). Metabolites were quantified with LCModel (4) 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 are reported. To account for any atrophy, concentrations were corrected for the amount of CSF present in each VOI.

Results and Discussion

Comparable spectral quality was obtained in controls and patients (Fig. 1; p values for signal-to-noise ratio and linewidth = 0.2 - 0.8 in the 3 VOI). Mild vermian atrophy in patients was implied by an increased CSF content of the VOI (17% in patients vs. 10% in controls, p = 0.01), but was not substantial enough to degrade signal-to-noise in patients vs. controls. NAA and glutathione were decreased in the cerebellar hemispheres of patients (Fig. 2), likely indicative of cell death in deep cerebellar nuclei and reduced antioxidant defenses, respectively. Patients were distinguished from controls when NAA vs. glutathione values in the hemispheres of each participant were plotted (Fig. 3). NAA and glutamate were decreased in the vermis of patients (Fig. 2). Glutamate reduction is in excellent agreement with postmortem findings (5). The same alterations were observed in spectra averaged over all patients vs. controls. No changes were detected in the pons consistent with sparing of this structure in FRDA.

This is the first report of a significant reduction of glutathione in patients suffering from a neurodegenerative disease and establishes the feasibility of simultaneously assessing antioxidant and neuroaxonal status in these conditions by ^{1}H MRS at 4 T.

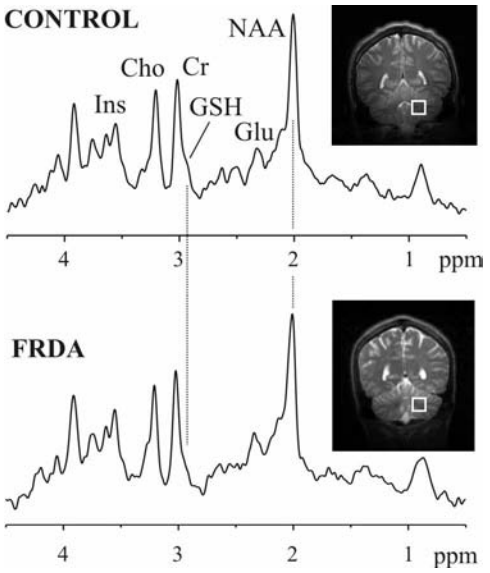

Fig. 1. Spectra acquired from the cerebellar hemispheres of a patient with FRDA and a healthy volunteer. M*yo*-inositol (Ins), choline (Cho), creatine (Cr), glutamate (Glu), N-acetylaspartate (NAA) are indicated. One of the areas that the glutathione (GSH) signal contributes to is also marked. Voxels (4.9 ml) are shown on T_2-weighted images.

References

1. Taroni F & DiDonato S, *Nat Rev Neurosci*, 5: 641, 2004. **2.** Piemonte F et al, *Eur J Clin Invest*, 31:1007, 2001; Pastore A et al, *JBC*, 278:42588, 2003. **3.** Tkáč I et al, *Appl Magn Reson*, 29: 139, 2005. **4.** Provencher SW, *MRM*, 30, 672, 1993. **5.** Huxtable R et al, *Can J Neurol Sci*, 6:255, 1979.

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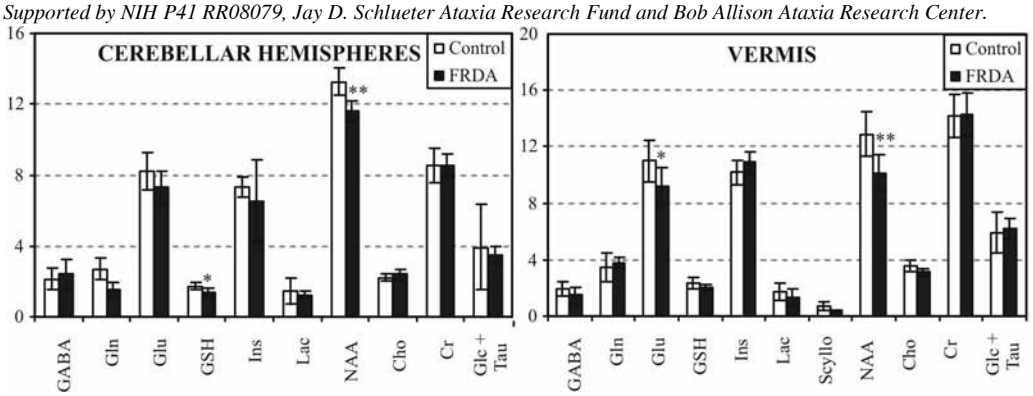

Fig. 2. Average (± SD) metabolite concentrations (μmol/g) in controls (N=7 for cerebellar hemispheres, N=11 for vermis) and patients with FRDA (N=5). GABA: γ-aminobutyric acid, Gln: glutamine, Glu: glutamate, GSH: glutathione, Ins: *myo*-inositol, Lac: lactate, Scyllo: *scyllo*-inositol, NAA: N-acetylaspartate + N-acetylaspartylglutamate, Cho: choline-containing compounds, Cr: creatine + phosphocreatine, Glc: glucose, Tau: taurine. *: $p < 0.05$, **: $p < 0.01$.

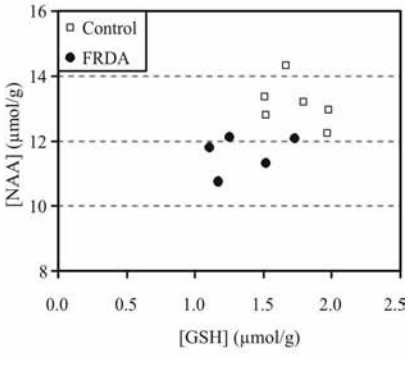

Fig. 3. Glutathione and NAA concentrations obtained from the cerebellar hemispheres of individual participants.