Friedreich's ataxia: an in vivo proton MR spectroscopy study of the cerebellum.

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Synopsis

Friedreich ataxia (FRDA) is the most common form of autosomal recessive spino-cerebellar ataxia. Cerebellar metabolism in nine FRDA patients, clinically evaluated with the ICARS scale, was studied using *in vivo* ^{1}H-MRS. Cerebellar [NAA] was significantly reduced in the FRDA patients compared to controls ($p<0.001$). In the patients cerebellar [NAA] showed a significant negative correlation with GAA1 ($r=-0.74$; $p<0.05$) and a more significant negative correlation with the total ICARS score ($r=-0.82$; $p<0.01$). ^{1}H-MRS can quantify the extent of neurodegeneration in FRDA and provides robust surrogate markers of disease progression that may be used in assessing the effect of pharmacological treatments.

Introduction

Friedreich ataxia (FRDA) is the most common form of autosomal recessive spino-cerebellar ataxia with a frequency of 1 in 50,000 live births. It is caused, in the vast majority of cases, by a GAA triplet expansion in the *FRDA* gene on chromosome 9q13. The *FRDA* gene product, frataxin, is a widely expressed mitochondrial protein which is severely reduced in FRDA patients (1-2). Pathological changes are most prominent in the dorsal root ganglia and posterior columns of the spinal cord, cerebellum, and cortico-spinal tract. In the cerebellum loss of dentate neurons is a prominent pathological finding. ^{1}H-MRS allows non invasive quantification of several brain metabolites including the neuronal marker N-acetyl-aspartate (NAA). Aim of this study was to identify, using ^{1}H-MRS, *in vivo* markers of neuro-degeneration in FRDA patients. Brain metabolic data were correlated with genotype, disease duration and severity, assessed by International Cooperative Ataxia Rating Scale (ICARS) (3).

Methods

Nine FRDA patients (7 males, age range 15-43 years) homozygous for the GAA expansion and eight sex- and age-matched healthy volunteers were studied. Patients were assessed neurologically using the ICARS scale by the same neurologist (CT). ^{1}H-MRS studies were performed in a 1.5T General Electrics Medical Systems (Milwaukee, Wisconsin) Signa Horizon LX whole-body scanner using a 25cm diameter quadrature birdcage head coil. MRI study included axial FSPGR (fast spoiled gradient echo) T1 images (slice thickness=3 mm, slice gap=0 mm, TE= 2.6 ms, TR=250 ms, matrix=256x256, FOV=24x24 cm). Voxel (volume: 6 cm^3) was placed in the left cerebellum including the dentate nucleus (figure 1). Single voxel ^{1}H-MRS spectra were acquired using the PRESS sequence. Absolute concentrations of NAA, creatine (Cr), choline (Cho) and myo-inositol (mI) were measured by acquiring spectra at 5 echo times (TE= 35, 70, 100, 144, 288ms; TR= 4000ms; number of acquisitions=64) and using water as internal standard (TE from 25 to 1000ms; TR = 15000ms). Peak area for NAA at 2.02 ppm, for Cr at 3.03 ppm, for Cho at 3.22 ppm, and mI at 3.56 ppm were calculated using the time domain fitting program AMARES/MRUI (http://carbon.uab.es/mrui). Peak integral values were expressed relative to the Cr peak. Statistical significance, determined by the Student *t* test for unpaired data, was taken as $p<0.05$. Linear regression analysis was used to calculate correlation coefficients.

Results: Patients' GAA triplet repeats in the smaller allele (GAA1) ranged from 270 to 768, the age at onset from 9 to 38 years, and the disease duration from 5 to 20 years. The total ICARS score ranged from 13/100 to 65/100. Cerebellar NAA content was significantly reduced in the FRDA patients compared to healthy controls ($p<0.001$) (figure 1). Patients' cerebellar [NAA] showed a significant negative correlation with GAA1 ($r=-0.74$; $p<0.05$) and a more significant negative correlation with the total ICARS score ($r=-0.82$; $p<0.01$) (Figure 2).

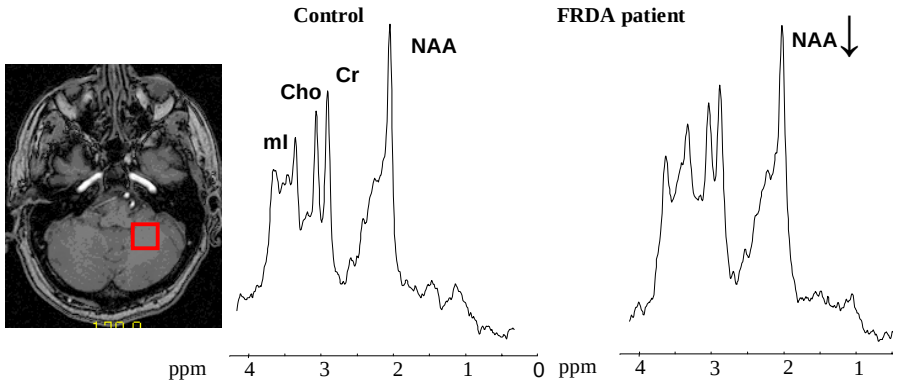

Figure 1. *Left*: Axial FSPGR T1 image (TE=2.6ms, TR=250ms) showing left cerebellum voxel localitation. *Centre and right*: ^{1}H-MRS spectra (TR=4000ms; TE=35ms) from a healthy volunteer and a FRDA patient.

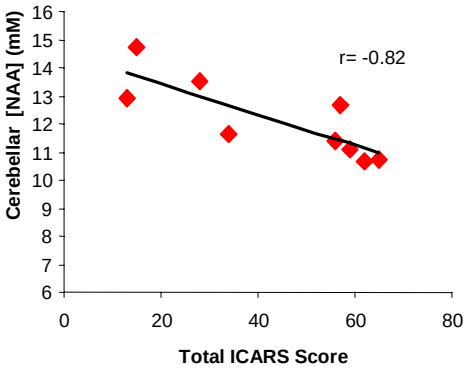

Figure 2. Correlation between cerebellar [NAA] and total ICARS score in FRDA patients.

Discussion

In accordance with neuropathological features, the neuronal marker NAA is reduced in the cerebellum of FRDA patients. The NAA concentration was more reduced in patients with the higher number of GAA repeats and, in particular, in patients with a more severe neurological impairment as assessed using the ICARS scale. These results show that ^{1}H-MRS can quantify *in vivo* the extent of neurodegeneration in FRDA and provides robust surrogate markers of disease progression that may be used in establishing the effect of pharmacological treatments (4).

References

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