Brain diffusion weighted imaging study of Friedreich ataxia patients

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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 homozygous 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). The size of the expansion in the smaller allele (GAA1) has a modulating effect on the age at onset and several phenotypic features of the disease (1). Pathological changes are most prominent in the dorsal root ganglia and posterior columns of the spinal cord, cerebellum, and cortico-spinal tract. DWI allows the spatially-resolved assessment of brain water apparent diffusion coefficient (ADC), which typically increases when neurodegeneration occurs (2). The aim of this study was to define the extent of the neurodegenerative brain damage in FRDA and to identify *in vivo* markers of neuro-degeneration. Brain DWI data were correlated with genotype and disease severity, assessed by International Cooperative Ataxia Rating Scale (ICARS) (3).

Methods

Nineteen FRDA patients (16 males/3 females, age 28±10 years, mean ± SD) homozygous for the GAA expansion, and 19 sex- and age-matched controls (15 males/4 females, age 29±8 years, mean ± SD) were studied. Disease severity was assessed using the ICARS by a single neurologist (CT).

Subjects were studied in a 1.5T General Electrics Medical Systems (Milwaukee, Wisconsin) Signa Horizon LX whole-body scanner. Axial DW images were obtained (thickness = 5 mm, inter-slice gap = 1 mm) using a single-shot EPI sequence (matrix size = 192 x 192 mm). As previously reported (2), orthogonal x, y, and z diffusion encoding gradients were applied with gradient strengths corresponding to b-values of 300, 600 and 900 mm^2/s. In addition, images without diffusion weighting were acquired corresponding to b = 0 s/mm^2 and exhibiting T_2-contrast.The apparent diffusion coefficient (ADC) of each direction was determined pixel-wise using a least-squares fit, assuming a signal attenuation depending mono-exponentially on the b-value. By calculating the mean of the three directions, the ADC trace map was generated.

Regions of interest (ROIs) were defined in the bulb, pons, left and right middle cerebellar peduncles (MCP), cerebellar white matter (WM), dentate, posterior limb (PL) of the internal capsule, thalamus, caudate, putamen, and pallidus. Histograms of ADC were generated for all pixels in the vermis and cerebellar hemispheres and the 50th percentile values calculated along with the mean using a well established technique (4).

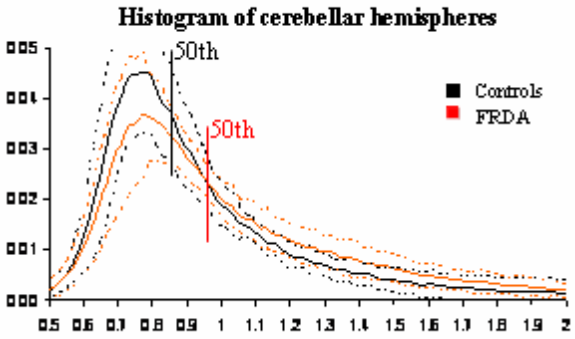
Statistical significance, determined by the Student test, was taken as $p<0.05$. Linear regression analysis was used to calculate correlation coefficients.

Results. Patients' GAA triplet repeats in the smaller allele (GAA1) ranged from 270 to 950, the age at onset from 3 to 38 years, and the disease duration from 5 to 25 years. The total ICARS score ranged from 13/100 (in the least affected patient) to 90/100 (in the most severely affected). In table 1and figure are reported the most significant differences between patients and controls in ADC values along with the correlations coefficients between ADC values and number of GAA1 repeats and total ICARS score.

ROIs	ADC (x10^{-3} mm^2/s)		*P#*	ADC vs GAA1	ADC vs ICARS
	Controls	FRDA			
BULB	0.82± 0.10	0.95± 0.11	0.003	r=0.64 *p*=0.003	r=0.54 *p*=0.01
MCP	0.82± 0.09	0.92± 0.09	0.004	r=0.53 *p*=0.01	r=0.61 *p*=0.001
Cerebellar WM	0.74± 0.06	0.79± 0.11	0.07	r=0.46 *p*=0.05	r=0.45 *p*=0.05
DENTATE	0.76± 0.05	0.81± 0.10	0.10	r=0.67 *p*=0.001	r=0.66 *p*=0.002
LOWER OPTIC RADIATION	0.82± 0.03	0.84± 0.04	0.07	r=0.51 *p*=0.02	r=0.74 *P*=0.0002
INTERNAL CAPSULE PL	0.71± 0.02	0.73± 0.04	0.2	r=0.74 *p*=0.0002	r=0.76 *p*=0.0002
VERMIS 50° percentile	0.97± 0.05	1.16± 0.15	0.0001	r=0.48 *p*=0.03	r=0.64 *p*=0.002
CEREB HEM. 50°percentile	0.86± 0.04	0.95± 0.11	0.002	r=0.50 *p*=0.02	r=0.75 *p*=0.0001

Table. Mean ADC values (± SD)in controls and FRDA patients and regression analysis with GAA1 and ICARS score

Figure. Histograms of ADC values in the cerebellar hemispheres Black lines = healthy subjects; red lines = patients; solid lines = mean values; dotted lines = standard deviation. i.n.u. = integral normalised units



Discussion

In accordance with the neuropathological features, ADC values were increased in the bulb and cerebellum of FRDA patients and correlated with the GAA1 repeats and, in particular, the ICARS score. In the dentate, cortical-spinal tract, and optic radiation of FRDA, where ADC increase just failed to reach a statistical significance, ADC values were clearly modulated by the number of GAA1 repeats and the disease severity, as assessed by the ICARS scale. These results show that DWI is a suitable non-invasive technique to quantify the extent of neurodegeneration in FRDA providing biomarkers of disease progression for the evaluation of therapeutic interventions.

References

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