Brain diffusion-weighted imaging in Friedreich's ataxia

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Introduction

Friedreich ataxia (*FRDA*) is the commonest form of autosomal recessive spino-cerebellar ataxia and is caused, in most cases, by a homozygous GAA triplet expansion in the *FRDA* gene on chromosome 9q13, leading to a decrease of frataxin protein (1). Pathological studies reported changes in the large peripheral sensory fibres, dorsal root ganglia, posterior roots and posterior columns of spinal cord, pyramidal tract, and cerebellum (1). MRI may disclose atrophy of the spinal cord and medulla and more rarely cerebellum. Two studies, using DWI (2) and DTI (3) in small samples of patients, revealed increased diffusivity (MD) and/or reduced fractional anisotropy (FA) at the level of brainstem, cerebellar WM and internal capsule, as well as in some other sovra-tentorial white matter regions. Our aim was to use DWI to systematically evaluate the extent and distribution of brain changes in a large series of *FRDA* patients. MD was assessed extensively using ROI and histogram methods. The relationship between MD values and genetic and clinical features was evaluated to identify the best DWI biomarkers of disease progression, for future assessment of pharmacological interventions in *FRDA*.

Methods

27 *FRDA* patients (17 males, age 30±12, mean ± SD) homozygous for a GAA expansion and 21 healthy volunteers (16 males, age 30±10) were studied. Disability was quantified using the ICARS score. Subjects were studied in a 1.5 T General Electrics Medical Systems (Milwaukee, Wisconsin) Signa Horizon LX whole-body scanner. As previously reported (4), axial DW images were obtained (slice thickness = 5 mm, inter-slice gap = 1mm) using a single-shot EPI sequence with α = 90º, TR = 10 s, TE = 100 ms, an in-plane resolution of 1.66 mm, and phase encoding in right-left direction. Orthogonal x, y and z diffusion-encoding gradients were applied with gradient strengths corresponding to b-values of 300, 600 and 900 s/mm^2. In addition, images without diffusion weighting were acquired, corresponding to b = 0 s/mm^2 and exhibiting T_2 contrast. ROIs were selected manually on T_2-weighted EPI images and were defined to include medulla, pons, left and right middle and superior cerebellar peduncle (MCP, SCP), dentate nucleus, cerebellar white matter, thalamus, caudate, putamen, pallidus, pyramidal tract at the level of the posterior limb of internal capsule (PLIC), optic radiation (OR) and corpus callosum. For a global evaluation of brain MD, histograms of MD were generated for all pixels in the sovratentorial and infratentorial compartments (Fig. 1-A). As previously described (5) infratentorial compartment histograms of MD were also generated separately for areas corresponding to brainstem, vermis, and cerebellar hemispheres determined by manual segmentation (Fig. 1-B), yielding 50th percentile values (medians). Student t-test for group comparisons and Pearson test for correlations were used accepting P<0.05 as significant.

Results

The *FRDA* patients had significantly higher MD values than controls in the medulla (P < 0.001), pons (P = 0.01), MCP (P < 0.001), SCP (P < 0.001), pyramidal tract at PLIC level (P = 0.02), and OR (P < 0.001), as well as higher median MD values at the level of the infratentorial structures such as brainstem (P < 0.001), cerebellar hemispheres (P < 0.001) and especially in the cerebellar vermis (P < 0.001). Overall, the *FRDA* patients had an increased median MD value in the whole sovratentorial compartment (P = 0.004) (Table). MD values were strongly correlated with the number of GAA repeats in the smaller allele (GAA1), age at onset, disease duration and in particular with ICARS score. In all brain regions total ICARS scores correlated with MD values, with r values ranging from 0.44 (MCP) to 0.73 (cerebellar hemispheres). Regarding GAA1 repeats higher correlations were found in pyramidal tract (r = 0.74), medulla (r = 0.46), and OR (r = 0.47). (Fig. 2)

Discussion

The main findings of our study were: 1) in *FRDA* patients the neurodegenerative damage is more widespread than previously shown by pathological and MRI studies with a clear involvement not only of infratentorial but also of sovratentorial structures; 2) MD values in *FRDA* patients showed a highly significant correlation with clinical variables: in particular, in all brain structures with abnormal diffusion, MD values were higher in patients with higher ICARS total scores; 3) the correlation between GAA1 triplet number and MD values was in general weaker than for total ICARS score, long white matter tracts showing the highest correlation coefficients. In conclusion, our study showed that DWI is a suitable non-invasive technique to quantify the extent of neurodegeneration in *FRDA* and that may be used to provide biomarkers of disease progression for the evaluation of therapeutic interventions.

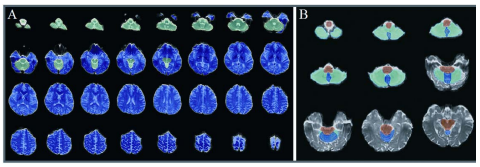

Figure 1. Manual segmentation of areas for histogram analysis. A: sovratentorial compartment (blue) and infratentorial compartment (green); B: brainstem (red), cerebellar vermis (blue) and cerebellar hemispheres (green).

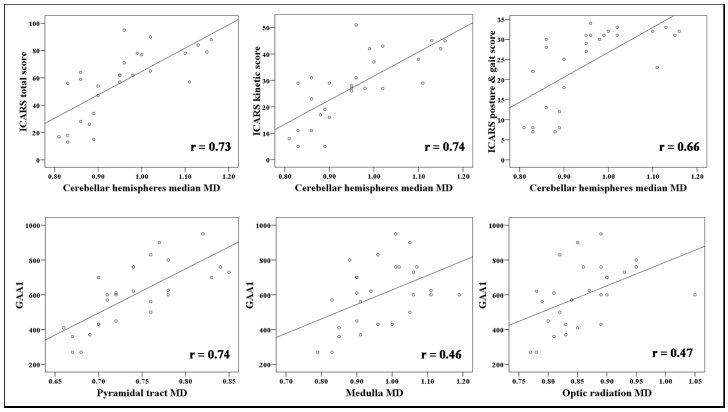

Figure 2. Correlation between ICARS total score and subscores *vs* cerebellar hemispheres median MD (upper row) and between the GAA1 repeats *vs* pyramidal tract MD, medulla MD and optic radiation MD values (lower row) in *FRDA* patients.

References

1. Pandolfo M (2008). *Arch Neurol*. 65:1296-1303
2. Della Nave R et al (2004) *Neuroimage*. 22:698-705.
3. Della Nave R et al (2008) *Neuroimage*. 40:19-25.
4. Rizzo G et al (2008) *Brain*. 131:2690-2700.
5. Martinelli P et al (2007) *Mov Disord*. 22:1182-1185.

Table. MD values in the FRDA patients and in healthy controls. Values are reported as mean and standard deviation

ROIs	FRDA MD (x10^{-3} mm^2/s)	Controls MD (x10^{-3} mm^2/s)	*P#*
Medulla	0.96±0.10	0.81±0.08	***<0.001***
Pons	0.94±0.14	0.85±0.06	***0.01***
MCP[a]	0.90±0.11	0.79±0.06	***<0.001***
SCP[a]	0.88±0.08	0.78±0.04	***<0.001***
Dentate nucleus[a]	0.79±0.11	0.75±0.05	0.20
Cerebellar white matter[a]	0.77±0.09	0.73±0.05	0.06
Caudate nucleus[a]	0.78±0.05	0.78±0.04	0.98
Putamen[a]	0.74±0.03	0.73±0.02	0.23
Pallidus[a]	0.77±0.07	0.75±0.05	0.24
Thalamus[a]	0.78±0.03	0.78±0.03	0.26
Pyramidal tract at PLIC[a]	0.74±0.05	0.71±0.03	***0.02***
Optic radiation[a]	0.86±0.06	0.79±0.02	***<0.001***
Corpus Callosum[b]	0.80±0.06	0.77±0.05	0.06
HISTOGRAM ANALYSIS			
Brainstem median	0.96±0.07	0.89±0.04	***<0.001***
Cerebellar hemispheres median	0.95±0.10	0.85±0.04	***<0.001***
Vermis median	1.18±0.16	0.97±0.06	***<0.001***
STC median	0.88±0.05	0.85±0.02	***0.004***