Optic radiation impairment in Friedreich ataxia: a diffusion-weighted imaging and neurophysiological study

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Introduction

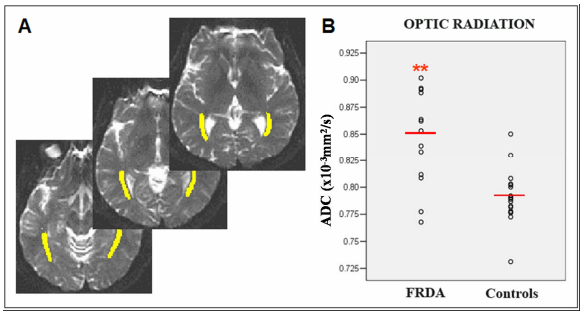
Friedreich Ataxia (FRDA) is the commonest form of hereditary ataxia with autosomal recessive transmission (1). It is caused by a lack of the mitochondrial protein frataxin (FXN) (2), associated with a GAA triplet expansion in the first intron of the FXN gene located on chromosome 9q13-q21.1 (3). Optic impairment is common in mitochondrial disorders (4). Its occurrence in FRDA has been recognized for a long time, but poorly characterized (5). Diffusion-weighted imaging (DWI), which can disclose increased water apparent diffusion coefficient (ADC) in brain areas where axonal loss occurs, and visual evoked potentials (VEPs) were used to look for evidence of visual pathway involvement in FRDA patients.

Methods

We recruited thirteen patients with a genetically confirmed diagnosis of FRDA and eighteen age-matched healthy volunteers. Clinical symptoms were evaluated using the International Cooperative Ataxia Rating Scale (ICARS) (6). Subjects were studied in a 1.5T General Electrics Medical Systems (Milwaukee, Wisconsin) Signa Horizon LX whole-body scanner. Axial DW images (thickness = 5 mm, inter-slice gap = 1 mm) were obtained using a single-shot EPI sequence (matrix size = 192 x 192 mm). 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 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 map was generated.

Regions of interest (ROI) included left and right optic radiations (Figure 1-A), localized following landmarks indicated by recent imaging studies (7,8). Pattern reversal visual evoked potentials (P-VEPs) to stimulation with 31' checks and with 15' checks and Flash-electroretinograms (F-ERG) were recorded. Statistical analyses were performed using nonparametric tests with SPSS 12.0 for Windows, assuming a significant *P*-value <0.05. The Mann-Whitney U test was used to evaluate differences among two groups. For correlations we used the Spearman rank test.

Figure 1. A: ROIs including optic radiation. B: scatter plot of values of two groups (**= < 0.01).



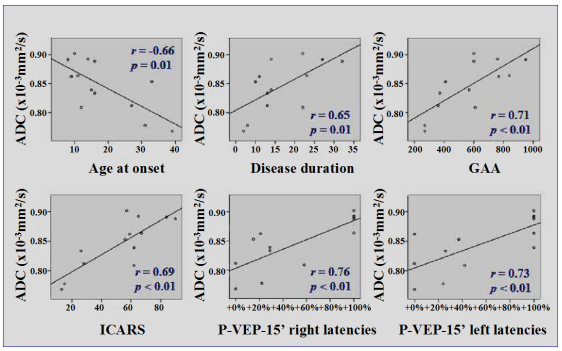


Figure 2. Correlations between ADC values and age at onset, disease duration, GAA expansion, ICARS score and P-VEP-15' latencies.

	FRDA patients (13)	Controls (18)	*P (M-W test)*
Optic radiation	0.85 +/- 0.04	0.79 +/- 0.02	< 0.01

Table. Mean ADC values of optic radiation in patients and controls.

Results

Four patients reported visual symptoms. P-VEPs differed from normal values in seven and eleven out of thirteen patients with 31' and 15' checks stimulation respectively. Cortical response was absent in five patients bilaterally with 15' checks stimulation. Delayed latency of the P100 component was the most frequent abnormality, and was increased by 21-86% in six patients. Five of those also showed reduced amplitude. F-ERG was normal in all patients. The FRDA patients had significantly higher ADC values in the optic radiations than healthy subjects ($p < 0.01$) (Table; figure 1-B). ADC values in the optic radiation correlated with age at disease onset ($r = -0.66$; $p < 0.01$), disease duration ($r = 0.65$; $p < 0.05$), GAA triplet expansion (r = 0.71; $p < 0.01$), total ICARS score ($r = 0.69$; $p < 0.01$) and all neurophysiological parameters, particularly P-VEPs-15' latencies ($r = 0.76$ dx / 0.73 sn; $p < 0.01$) (Figure 2).

Discussion

As in other mitochondrial disorders, visual pathway involvement is common in FRDA (4,5). Few patients reported clear symptoms, but subclinical VEP abnormalities were disclosed in most subjects. DWI data provided evidence of microstructural damage of the optic radiations in FRDA patients and ADC values correlated with age at disease onset, disease duration, GAA triplet expansion, total ICARS score and all neurophysiological parameters.

Our study suggests that neurodegenerative changes in the posterior section of the visual pathway contribute to clinical and neurophysiological visual involvement in Friedreich Ataxia.

References

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