Brain diffusion-weighted imaging in Friedreich's ataxia

G. Rizzo1,2, C. Tonon1, M. L. Valentino2, D. N. Manners3, F. Fortuna1,2, C. Geller1, A. Pin1, S. Ghezzo1, A. Baruzzi1, C. Testa1, E. Malucelli1, B. Barbirioli1, V. Carelli1, and R. Lodi3

1MR Spectroscopy Unit, Department of Internal Medicine, Aging and Nephrology, University of Bologna, Bologna, BO, Italy, 2Neurological Sciences, University of Bologna, Bologna, BO, Italy, 3U.O. Biochemistry and Genetics, Fondazione IRCCS-Istituto Neurologico Nazionale “Carlo Besta”, Milano, MI, Italy, 4Neuropsychiatric Unit, Ospedale Maggiore, Bologna, BO, Italy

Introduction

Friedreich ataxia (FRDA) is the commonest form of autosomal recessive spino-cerebellar ataxia and is caused, in most cases, by a homoyzous 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) Sigma 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 = 90°, 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/mm². In addition, images without diffusion weighting were acquired, corresponding to b = 0 s/mm² and exhibiting T2 contrast. ROIs were selected manually on T2-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)"