Potential neuroimaging biomarkers validated in Friedreich's ataxia: DTI and functional magnetic resonance findings

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Background: Friedreich's ataxia (FRDA) is a progressive hereditary neurodegenerative condition caused by an autosomal recessively inherited GAA repeat in the FXN gene. In this study we used clinical measures and advanced tractography combined to functional MRI (fMRI) to explore white matter (WM) connectivity and motor dysfunction in a cohort of FRDA patients.

Methods: Molecularly defined FRDA patients (n=17) were clinically assessed with the specific ataxia scales. Patients and age matched healthy controls underwent a neuroimaging study protocol on a 3T MRI scanner that included advanced neuroimaging DTI and fMRI. After the pre-processing, a nonlinear monoexponential model was used to calculate fractional anisotropy (FA), mean, radial and axial diffusivity (MD, RD, AD) maps. Non-parametric voxel-based permutations were performed on the WM maps regions of interest (ROI), considering age and sex via a general linear model (GLM) with critical threshold 0.05 while correcting for multiple tests. An fMRI sequence was acquired during a simple block design finger-tapping task. After a standard pipeline pre-process, intra- and intergroup GLM analysis were conducted, considering age and sex variables and also $p < 0.001$ threshold.

Results: Our cohort included early onset FRDA patients, mean age at onset 10.65 ± 5.08 (range 4-20 years); F/M: 13/4; mean GAA expansion in the smaller repeat was 651,07 ± 234.39 (n=16) and one patients with a single base pair deletion and 170 GAA repeat. Mean age at assessment was 27.82 ± 10.51years (12-51), mean disease duration was 17.17 ± 8.43 (4-33). The mean age of the control group was 23 ± 4.83 years; F/M= 5/8. From both the voxel-based and ROI-based analysis altered FA and MD parameters were consistently found in the following four Central Nervous System areas: cerebellar WM (superior, median and inferior peduncles), long sensory-motor pathways (corticospinal and lemnisceal systems, cerebral peduncles), major commissural fibres (splenium and tapetum of the corpus callosum), the thalamic and the optic radiations. The fMRI data were analyzed from 13 patients (mean age 30.05 ± 11.76 years) and 8 controls (mean age 24.5 ± 3.85 years). The finger-tapping task demonstrated intragroup activation of the controlateral motor cortex and the ipsilateral cerebellar cortex both in patients and healthy controls. Intergroup analysis demonstrated a consistent and significantly higher cerebellar cortex activation, in controls compared to the FRDA patients, in particular in the lobules V and VI.

Discussion: We show that a comprehensive MRI protocol consistently discriminates FRDA patients from controls. DTI changes in selected areas and BOLD signal in the cerebellar ipsilateral cerebellar cortex in response to a simple motor task show strong intergroup discriminating power and may prove to be useful paraclinical disease markers. A longitudinal study is undergoing to explore the sensitivity of these indicators to disease progression.