

FIBER BUNDLE ATROPHY IN FRIEDREICH'S AND SPINOCEREBELLAR ATAXIA

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Introduction

Friedreich's ataxia (FRDA) and spinocerebellar ataxia (SCA; type 1 and 2) are inherited diseases that requires molecular genetic tests to be diagnosed. From neuropathological examinations, although rare, it is known that FRDA is characterized by atrophy of the spinal cord, secondary degeneration of the dorsal medulla, and loss of neurons in the dentate nuclei; whereas SCA presents a pattern of macroscopic olivopontocerebellar atrophy. Aim of this study was to investigate the pattern of fiber bundle atrophy at a voxel level. We used a method (1) which relies on the production of anisotropy maps derived from diffusion tensor (DT) images to contrast fiber bundles, and on a non-linear registration to calculate differences in comparison with an atlas.

Methods

Thirty-six patients were enrolled: 16 FRDA (mean age=30 years, range=13-38 years, M/F=7/9), 10 SCA type 1 (mean age=47 years, range=36-76 years, M/F=3/7), and 10 SCA type 2 (mean age=47 years, range=28-68 years, M/F=7/3). In addition, 15 healthy subjects (mean age=38 years, range=26-66 years, M/F=10/5) served as controls, and 20 further healthy subjects (mean age=31 years, range=35-44 years, M/F=14/6) were used for the production of the reference atlas. A pulsed-gradient spin-echo single shot echo-planar sequence (PGSE-SS-EPI) (TR=9540 ms, TE=89 ms), with diffusion-encoding gradients applied in 15 non collinear directions (b factor=1000 s/mm²) was acquired using a 1.5 Tesla scanner (Philips, Intera). Fifty contiguous axial slices, with 3 mm slice thickness, 128x128 matrix, 256 mm field of view and 3 NEX were used.

DW images were first corrected for distortion induced by eddy currents; then the DT was estimated by linear regression (2) and fractional anisotropy (FA) maps calculated (3). Healthy subjects from the reference group were used for the production of an FA atlas of the average morphometry: a single control subject's FA image was chosen randomly as a temporary atlas, and all other FA images were then registered to it using a non-linear deformation algorithm (4). The average of the registered FA images were re-sampled with the inverse of the average deformation field to achieve a morphological (shape) mean as well as an intensity (FA) mean of the group. The new average image was used as a target atlas during the next iteration. To reduce the influence of the first template on the final atlas, three iterations were used to create the final FA atlas (5). The non-linear transformation between FA maps of all subjects and the atlas was then calculated and the determinant of the jacobian of the transformation calculated; this scalar summarizes the point-wise volume changes produced by the deformation: values less than unity reflect atrophy, whereas values greater than unity reflect hypertrophy. As a further step, the same analysis was carried out by considering the cerebellum only. For this purpose, the cerebellum was first segmented from the atlas by manually tracing the peripheral contours. Then, a preliminary segmentation of the cerebellum was achieved by deforming the cerebellum mask back to the single subject space, and then by manual refinement. Determinant jacobian maps from both the analyses were smoothed with a 4 mm gaussian filter, before entering the statistical analysis.

An ANOVA model (6) was used to predict at a voxel level the changes between each group of patients and the controls, adjusting for age and sex. Threshold of statistical significance was set with the False Discovery Rate correction (7) at $p < 0.05$.

Results

Whole brain analysis: compared to controls, all the three patient groups showed atrophy in the pons and in the medulla, with the additional involvement of the middle cerebellar peduncles in SCA1-2 patients and the cerebral peduncles in SCA2 patients, only. In SCA1-2 patients, atrophy was also detected in the WM region surrounding the precentral gyrus.

Cerebellum analysis: compared to controls, all the three patient groups were more atrophic in the pons; in addition, FRDA patients were also characterized by a greater atrophy of the inferior cerebellar peduncles and the pyramids, and SCA2 patients of the middle cerebellar peduncles (Figure).

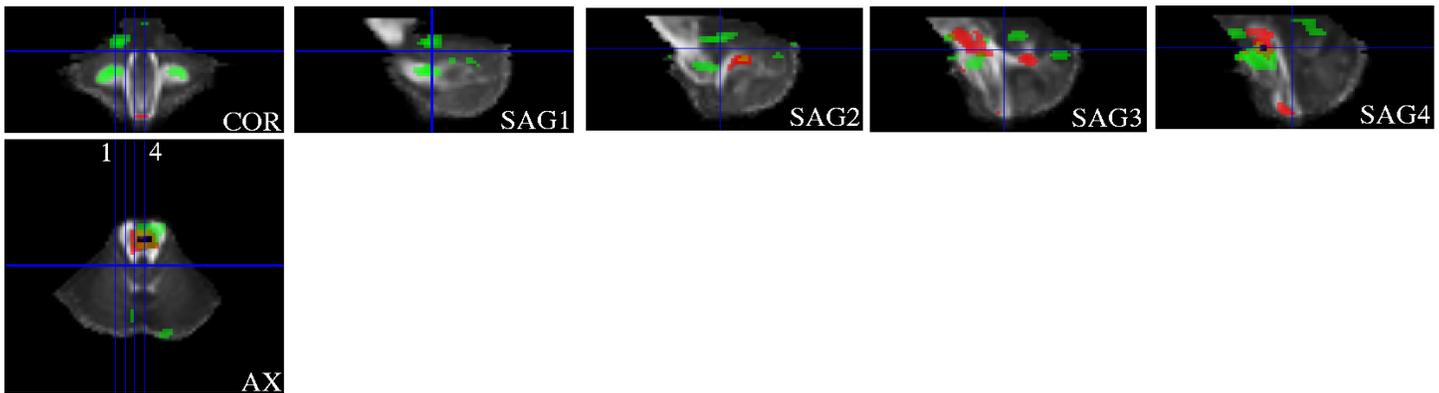


Figure. Atrophy distribution in the cerebellum: regions showing a significant atrophy from the comparisons between each patient groups vs. controls (FRDA: red; SCA1: blue; SCA2: green). Supra-threshold t values ($p < 0.05$ corrected with False Discovery Rate) are mapped over the FA template and showed in orthogonal views (cor, ax, sag1) and three more sagittal cuts (sag 2, 3,4).

Conclusions

The approach used was able to detect fiber bundle atrophy in FRDA and SCA1-2 patients, which agrees with pathological observations. The spatial distribution of atrophy was even better differentiated for each group when the cerebellum only was studied. This suggests that our approach might be useful to monitor disease evolution in this neurodegenerative conditions.

References

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