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Brain white matter tracts degeneration in Friedreich ataxia. An in vivo MRI study using tract-based spatial statistics and voxel-based morphometry

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Background and purpose: **Neuropathological examination in Friedreich ataxia (FRDA) reveals neuronal loss in the gray matter (GM) nuclei and degeneration of the white matter (WM) tracts in the spinal cord, brainstem and cerebellum, while the cerebral hemispheres are substantially spared. Tract-based spatial statistics (TBSS) enables an unbiased whole-brain quantitative analysis of the fractional anisotropy (FA) and mean diffusivity (MD) of the brain WM tracts in vivo.**

Patients and methods: **We assessed with TBSS 14 patients with genetically confirmed FRDA and 14 age- and sex-matched healthy controls who were also examined with voxel-based morphometry (VBM) to assess regional atrophy of the GM and WM.**

Results: **TBSS revealed decreased FA in the inferior and superior cerebellar peduncles and the corticospinal tracts in the medullary pyramis, in WM tracts of the right cerebellar hemisphere and in the right occipito-frontal and inferior longitudinal fasciculi. Increased MD was observed in the superior cerebellar peduncles, deep cerebellar WM, posterior limbs of the internal capsule and retrolenticular area, bilaterally, and in the WM underlying the left central sulcus. Decreased FA in the left superior cerebellar peduncle correlated with clinical severity. VBM showed small symmetric areas of loss of bulk of the peridentate WM which also correlated with clinical severity.**

Conclusions: **TBSS enables in vivo demonstration of degeneration of the brainstem and cerebellar WM tracts which neuropathological examination indicates to be specifically affected in FRDA. TBSS complements VBM and might be a more sensitive tool to detect WM structural changes in degenerative diseases of the CNS.**

Keywords: DWI; Tract-based spatial statistics; Gait disorders/ataxia; Friedreich ataxia

Introduction

Friedreich ataxia (FRDA) is the most common inherited ataxia and in most cases is due to a GAA repeat expansion in a gene on chromosome 9q13 coding for a mitochondrial protein named frataxin (Klockgether, 2000). Neuropathological studies show that FRDA is characterized by neuronal loss and WM tracts degeneration in the spinal cord, brainstem and cerebellum (Lowe et al., 1997). MRI studies in FRDA patients pointed out atrophy of the cervical spinal cord and dorsal medulla, of the GM in the rostral vermis and infero-medial portions of the cerebellar hemispheres and of the WM in the peridentate regions (Della Nave et al., 2007; Schols et al., 1997; Wullner et al., 1993; Huang et al., 1993). No signal change, notably with a tract distribution, was reported in the brain of patients with FRDA, but using a T2*-weighted sequence Waldvogel et al. (1999) reported abnormally increased T2* relaxation rate assumed to reflect increased iron content in the dentate nuclei of the cerebellum. Conversely, the atrophy of the spinal cord is combined with symmetric hyperintensity in proton density and T2-weighted images of the WM tracts in the lateral and posterior columns of cervical spinal cord reflecting wallerian

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degeneration in the cuneatus, gracilis and spinocerebellar tracts (Mascalchi et al., 1995).

In last years the capability of diffusion tensor MR images (DTI) to demonstrate the WM tracts has found increasing application for the structural evaluation of the normal and abnormal brain (Mori and Zhang, 2006). Recently, a voxel-wise analysis of multi-subject diffusion tensor data named tract-based spatial statistics (TBSS) was developed (Smith et al., 2006, 2007).

We hypothesized that TBSS could demonstrate in vivo the degenerating WM tracts in the brain of patients with genetically proven FRDA. Moreover we compared the sensitivity of TBSS in revealing structural damage of the brain WM tracts with that of voxel based morphometry (VBM) in detecting brain GM and WM atrophy in the same patients.

Patients and methods

Between March 2006 and April 2007 fourteen consecutive outpatients (9 women, 5 men, mean age 31±9 years) with genetically proven FRDA regularly followed at the ambulatories for ataxic diseases of the Neurological Department of the University of Florence, Siena and Bologna gave their informed consent to participate in this prospective study which was approved by the Ethical Committee of the University of Florence.

Molecular diagnostic methods were previously reported (Bidichandani et al., 1998) and the cut-off number of triplets repeats expansion qualifying for diagnosis was 100 GAA on both alleles for FRDA.

On the day of the MR examination, the same neurologist blind to the results of MR defined the patient's disease duration and computed her or his scores on the Inherited Ataxia Clinical Rating Scale (IACRS) (Filla et al., 1990). The IACRS is a 0–46 semi-quantitative scale with 46 corresponding to maximal clinical deficit which evaluates signs and symptoms related to ataxia, pyramidal tract dysfunction and impaired vibration or position sense. Mean disease duration was 17 years (range 5–31) and mean IACRS score was 27 (range 9–36).

Fourteen healthy volunteers (5 women and 9 men; mean age 31±6 years) without personal of familial history of neurological disease served as controls.

MR examination

Patients and controls underwent MR imaging examination in a single center on a 1.5 T system (Philips Intera, Best The Netherland) with 33 mT/m maximum gradient strength and SENSE coil technology. After scout and axial proton density and T2-weighted images (TR=2000 ms, TE 20/120 ms, FOV=256 mm, matrix size 256×288, 20 slices, slice thickness=5 mm, NEX=2), axial DTI with single-shot echo planar imaging sequence (TR=9394 ms, TE=89 ms, FOV=256 mm, matrix size=128×128, 50 slices, slice thickness=3 mm, no gap, NEX=3) was also acquired on axial plane for TBSS. Diffusion sensitizing gradients were applied along 15 non-collinear directions using b value of 0 (b_0 image) and 1000 s/mm^2. Maps of fractional anisotropy (FA) and mean diffusivity (MD) were calculated from the DTI after both automatic segmentation of the brain from the non-brain tissue and eddy currents correction by means of FDT 1.0 (FMRIB's Diffusion Toolbox 1.0 (Behrens et al., 2003) part of FSL 3.3; FMRIB Image Analysis Group, Oxford, UK) (Smith et al., 2004).

To assess regional atrophy, patients and controls were also examined with axial 3D T1-weighted turbo gradient echo [repetition time (TR)=25 ms, echo time (TE)=4.6 ms, flip angle=30°, field of view (FOV)=256 mm, matrix size=256×256, 160 contiguous slices, slice thickness=1 mm] images for VBM.

Data processing

Image data processing was performed on a PC running FMRIB Software Library (FSL) 3.3 package (FMRIB Image Analysis Group, Oxford, UK) (Smith et al., 2004) and the statistical parametric mapping 2 (SPM2) software (Wellcome Department of Cognitive Neurology, London, UK).

Preliminarily proton density and T2-weighted images were subjectively evaluated for focal abnormalities which can influence TBSS results. Moreover DTI and T1-weighted images were evaluated for motion artifacts before entering image processing.

TBSS analysis was performed using TBSS 1.0 tool part of the FSL 3.3 and is described in detail elsewhere (Smith et al., 2006, 2007). In brief, TBSS implies a four-step approach: identification of a common registration target and alignment of all subject's FA images to this target, creation of the mean of all aligned FA images and of a skeletonized mean FA image which is thresholded, projection of each subject's FA image onto the skeleton, voxel-wise statistic analysis across subject on the skeleton-space FA data. Using the same nonlinear registration, skeleton and skeleton projection vectors derived from the FA analysis, MD data were projected onto the skeleton before voxel-wise statistic analysis across subject (Smith et al., 2007).

The methodology of VBM closely followed that previously reported (Good et al., 2001) and included six steps: reorientation according to the antero-posterior commissure line, template creation to improve brains segmentation, normalization, segmentation in 3 classes of tissue (GM, WM and CSF), smoothing with a 8 mm full width half-maximum Gaussian kernel, and voxel-wise between groups statistical analysis.

Statistical methods

TBSS

Group comparison for FA and MD data was performed using permutation-based nonparametric inference on cluster size (Nichols and Holmes, 2002) and Randomise software part of FSL 3.3. A restrictive statistical thresholds was used (cluster-based thresholding $t>3$, $p<0.05$, corrected for multiple comparisons) (Smith et al., 2006).

In addition, only in FRDA patients we correlated FA and MD with each patient's IACRS score using the same software and permutation-based nonparametric inference on cluster size ($t>3$, $p<0.05$ corrected) (Smith et al., 2006).

Identification of the abnormal WM tracts revealed by TBSS was based on the Atlas made by Wakana et al. (2004) and the Testut and Latarjet's (1971) textbook of anatomy.

VBM

Statistical analysis of the MR data was based on the general linear model and the theory of Gaussian random fields. A voxel-wise comparison of spatially normalized T1-weighted images was made using SPM2. Group comparisons were performed by means of analysis of covariance (ANCOVA) using the total volume of each segmented image (GM volume for GM analysis, WM volume