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Tremor and Other Hyperkinetic Movements

Brief Reports

White Matter Microstructure in Idiopathic Craniocervical Dystonia

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Abstract

Background: Dystonias are hyperkinetic movement disorders characterized by involuntary muscle contractions resulting in abnormal torsional movements and postures. Recent neuroimaging studies in idiopathic craniocervical dystonia (CCD) have uncovered the involvement of multiple areas, including cortical ones. Our goal was to evaluate white matter (WM) microstructure in subjects with CCD using diffusion tensor imaging (DTI) analysis.

Methods: We compared 40 patients with 40 healthy controls. Patients were then divided into subgroups: cervical dystonia, blepharospasm, blepharospasm + oromandibular dystonia, blepharospasm + oromandibular dystonia + cervical dystonia, using tract-based spatial statistics. We performed a region of interest-based analysis and tractography as confirmatory tests.

Results: There was no significant difference in the mean fractional anisotropy (FA) and mean diffusivity (MD) between the groups in any analysis.

Discussion: The lack of DTI changes in CCD suggests that the WM tracts are not primarily affected.

Keywords: Craniocervical dystonia, idiopathic dystonia, blepharospasm, diffusion tensor imaging

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Introduction

Dystonias are hyperkinetic movement disorders characterized by involuntary muscle contractions that result in abnormal torsional movements and postures. Dystonia is often initiated or exacerbated by voluntary action and associated with excess muscle activation.[1] Blepharospasm (BSP) and cervical dystonia (CD) are the most common forms of adult-onset dystonia; the term craniocervical dystonia (CCD) encompasses all of those forms occurring either in isolation or in combination.[1–3]

Diffusion tensor imaging (DTI) works on the measurement of trends in random motion of water molecules in a given medium. This technique allows for the visualization of microstructures and quantifies water diffusion in tissues noninvasively. It is based on the theory that the water found in the tissues exhibits properties of anisotropic diffusion.[4] DTI provides information about the random displacement and passive diffusion of water molecules on the directionality and integrity of fibers. It can demonstrate neuronal loss through a decrease in diffusion anisotropy, shown by lower values of fractional anisotropy (FA) and higher values of mean diffusivity (MD). FA quantifies the preferred direction of diffusion of water molecules through white matter (WM) tracts, and MD represents the magnitude of the diffusion.[5–7] DTI also allows for the visualization of neural projections in the central nervous system.[8] The tract-based spatial statistics (TBSS) technique performs whole-brain analysis by measuring changes in water molecules in tissues and enables DTI sequence parameters to be compared using statistical analysis.[9,10]

Previous DTI studies in CCD produced conflicting results. In CD, DTI documented changes mainly in the circuit involving the cortex,

thalamus, basal ganglia, and cerebellum.[8,11–14] In turn, patients with BSP and blepharospasm + oromandibular dystonia (BOM) showed alterations in the cerebellum, parietal lobe, lentiform nucleus, thalamus, and insula.[15] There has never been a dedicated study of the WM in CCD; hence we performed DTI aiming to analyze the microstructure of WM in patients with CCD compared to healthy controls (HC).

Methods

Subjects

The Institutional Review Board of the University Hospital approved the study and all subjects signed an informed consent prior to participation in any study-related procedure. Patients were consecutively recruited from March 2010 until November 2013, at the Outpatient Movement Disorders Clinic, the Dystonia Clinic, and the Neurogenetics Service at the University of Campinas University Hospital.

A total of 108 patients were screened. 40 subjects presented idiopathic CCD were included: 5 subjects with isolated BSP (61.8 ± 10.3 years old), 9 with BOM (68.5 ± 5.0 years-old), 8 with BOM and CD (63.1 ± 11.1), and 18 subjects with isolated CD (52.8 ± 12.2). All subjects underwent a detailed review of their clinical history, family history, and treatment. A movement disorders specialist performed a neurological examination and assessed subjects on the Marsden–Fahn Scale.[16] The exclusion criteria were the presence of neurological abnormalities other than tremor; dystonia located in segments other than the craniocervical region; presence of significant clinical comorbidities; history of exposure to medications known to induce dystonia; abnormalities at neuroimaging; and known etiology of the dystonia syndrome. We excluded 68 patients with idiopathic or genetic dystonia presenting in sites other than the craniocervical area, or with secondary dystonia.

In addition, all subjects had a negative molecular test for *DYT1* and *DYT6* mutations.

We included 40 age- and sex-matched HC without a family history of dystonia and with a normal neurological examination. For each subject the same control was used for the total group analyses and the subgroup analyses (Table 1).

Since previous studies found differences as low as 0.016 in FA values to be significant,[17] we hypothesized a standard deviation of the difference of 0.03. For a sample of 40 subjects, the expected Statistical Power for those parameters would be 90%.

Magnetic resonance imaging (MRI) acquisition. Patients underwent magnetic resonance imaging (MRI) examination at the peak of action of the botulinum toxin (BoNT) to decrease the chance of motion artefacts.

The MRI protocol was as follows. Images were acquired in a 3T Intera Achieva-PHILIPS® (Best, The Netherlands) scanner, release 2.6.1.0, according to the following parameters:

- Diffusion tensor images with 32 gradient directions: 2 mm thick, repetition time (TR) 8,500, echo time (TE), 60; b-factor, 1,000; matrix, 256 × 256, and "field of view" (FOV) 256 × 256 mm;
- T1-weighted images with isotropic voxels of 1 mm, acquired in the sagittal plane (1 mm thick, flip angle 8°, TR 7.1, TE 3.2, matrix 240 × 240, and FOV 240 × 240 mm).

Table 1. Demographic Information

Dystonia (N)	Sex (Men%)	Groups	Mean Age ± SD	Mean Disease Duration (y) ± SD	Mean use of BoNT (y) ± SD
TOTAL (40)	30%	HC	56.0 ± 15.0	–	–
		P	59.5 ± 12.3	13.6 ± 6.9	9.5 ± 6.5
CD (18)	33,3%	HC	53.1 ± 12.7	–	–
		P	52.8 ± 12.2	15.4 ± 6.3	10 ± 6.0
BSP (5)	40%	HC	60.8 ± 10.1	–	–
		P	61.8 ± 10.3	10.6 ± 5.8	6.8 ± 4.1
BOM (9)	22,2%	HC	68.6 ± 3.8	–	–
		P	68.5 ± 5.0	13 ± 8.2	10 ± 8.0
BOM+CD (8)	25%	HC	63.0 ± 11.3	–	–
		P	63.1 ± 11.1	11.3 ± 6.0	9.1 ± 6.4

Abbreviations: BOM, Blepharospasm + Oromandibular; BOM+CD, Blepharospasm + Oromandibular Dystonia + Cervical Dystonia; BoNT, Botulinum Toxin; BSP, Blepharospasm; CD, Cervical Dystonia; HC, Healthy Controls; P, Patients; SD, Standard Deviation; y, Years.

Table 2. Mean FA Values per Group in the Confirmatory Analysis

Dystonia	Groups	Mean FA ± SD	P-Value
TOTAL	HC	0.46 ± 0.003	0.18
	P	0.47 ± 0.003	
CD	HC	0.47 ± 0.022	0.41
	P	0.47 ± 0.020	
BSP	HC	0.46 ± 0.015	0.62
	P	0.47 ± 0.025	
BOM	HC	0.45 ± 0.016	0.90
	P	0.45 ± 0.018	
BOM+CD	HC	0.47 ± 0.032	0.24
	P	0.45 ± 0.019	

Abbreviations: BOM, Blepharospasm + Oromandibular; BOM+CD, Blepharospasm + Oromandibular Dystonia + Cervical Dystonia; BSP, Blepharospasm; CD, Cervical Dystonia; FA, Fractional Anisotropy; HC, Healthy Controls; P, Patients; SD, Standard Deviation.

DTI analysis

TBSS. We compared all 40 patients with HC and then performed a subgroup analysis, based on dystonia body distribution.

Images were corrected for eddy currents using the eddycorrect tool from Oxford centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB)'s Diffusion Toolbox (FDT) (http://www.fmrib.ox.ac.uk/fsl/), which is part of the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL) software, version 4.1.4.

We obtained maps of FA using FDT. Voxelwise statistical analysis of the DTI data was carried out using TBSS. In summary, FA images were created by fitting a tensor model to the raw diffusion data using FDT, and then brain-extracted using the Brain Extraction Tool (BET). All FA data were aligned into a common space with the nonlinear registration tool (FNIRT), which uses a b-spline representation of the registration warp field. Following this, the mean FA image was created and thinned to generate a mean FA skeleton, which represents the center of all tracts common to the group. Each subject's aligned FA data were then projected into this skeleton and the resulting data fed into the voxelwise cross-subject statistics.[9,18] We performed a paired T-test to compare patients and HC, and the level of significance was set at 0.05. We performed an analysis using FSL randomise 10,000 permutations.[9]

Region of interest (ROI). We used ROI analysis[19,20] to confirm or refute our findings. This is based on obtaining the average FA values of all WM voxels. The DTI and the structural T1 weighted images (WI) of all patients were visually checked to find acquisition artefacts. The tensor calculation was performed with Explore DTI (A. Leemans, University Medical Center, Utrecht, The Netherlands) software.[21] For each subject, a native space FA map, a B0 map and an SPM8 (Statistical Parametric Mapping 8) deformation field file (native space–MNI) were created. The SPM8 new segment protocol was applied to the T1, aiming to generate normalized (MNI 152 (Montreal Neurological Institute - 152) WM probabilistic maps. The SPM8 deformation field and co-registration pipelines were used to match the WM maps with the native space DTI images. The resultant WM image of each subject was used to mask the FA maps and to calculate the average FA value of the total consistent WM area. Statistical analysis was performed via a paired T-test, first at the whole-group level and then at subgroup level, comparing the group of patients with HC.

Tractography. We also performed tractography as a confirmatory analysis, evaluating the total group only and extracting the FA/MD values.

The tensor calculation of all DTI was carried out with ExploreDTI[21] and fiber tractography using a semiautomatic deterministic methodology, briefly described below. ROIs to seed each tract were manually drawn on a normalized template. This template was created with non-diffusion weighted images of 10 local control subjects (mean age=33 years; age range=22–47 years; 50% females) acquired in the same MRI scanner, with the aim of improving anatomical matching to the study sample. Sequentially, the method employs the three-dimensional deformation field matrix of each subject to apply an inverse normalization operation (SPM8-deformation field algorithm), using the variants between native and standardized space to bring the normalized ROIs to that subject-specific space. Finally, the adjusted (native space) ROIs were used for the fiber tracking. Additionally, three ROIs designed to divide the brain in three heights in the axial plane were also transferred to each subject space. The resultant fiber

tracts were divided into three different regions, allowing verification of diffusion alterations along the fiber length.

We selected the pyramidal tract, due to previous findings of areas of atrophy in the motor cortex.[22] The tract was divided into inferior, middle and superior regions, and the DTI data were acquired bilaterally. We also selected other tracts with automatic segmentation implemented in the Neuroimaging Laboratory for this analysis: the body of the corpus callosum, brainstem, uncinate fasciculus, cingulum, fornix, and inferior occipitofrontal fasciculus. Statistical analysis was performed using a paired t-test, comparing the whole group of patients to the paired control group.

Results

Based on TBSS, there was no significant difference in FA/MD values between patients and HC, neither in the whole-group analysis nor in the subgroup analysis. ROI analysis showed no difference between FA values in either case (Table 2).

Tractography also revealed no changes in FA/MD in the total group. However, in the left inferior pyramidal tract there was a tendency of MD values to differ between groups ($p = 0.05$) (Tables 3 and 4).

Discussion

We performed an exploratory study to evaluate the whole WM in CCD compared to HC. We were aiming to uncover areas that might be involved but have not yet been studied. We found no significant difference between FA/MD values in any analysis.

There are few studies using DTI in CCD and the results have not been consistent. We employed different software to confirm and complement the results obtained with TBSS. First, we used TBSS, a known method that performs a full analysis of the brain by measuring water diffusion properties.[9] Second, we performed an ROI-based analysis, which uses well-established algorithms (ExploreDTI)[21] to obtain diffusion maps and an SPM8 new segment algorithm to isolate a WM probabilistic map. Despite both analyses being conceptually equivalent, the codes behind these techniques are completely independent, strengthening our findings. Finally, we conducted a tractography study on the whole group only and extracted FA/MD values for the pyramidal tract, body of corpus callosum, brainstem, uncinate fasciculus, cingulum, fornix, and inferior occipitofrontal fasciculus, which also did not uncover any significant differences in FA and MD values. Only the MD values in the inferior left pyramidal tract tended to differ. However, considering the small absolute difference in the values observed between the two groups and the large number of comparisons made, we did not consider this a valid result.

Our results may sound intriguing, but in light of the current literature, they are not necessarily controversial. DTI changes have not yet been observed in BSP compared to HC,[11,12] but a recent study including patients with BOM and BSP revealed FA reductions in the left anterior lobe of the cerebellum and the right precuneus of the parietal lobe, and increases in MD were detected in the right lentiform nucleus, thalamus, and insula.[15]

In CD, while some studies showed increased FA in the putamen, thalamus, brainstem, middle frontal and temporal gyrus, cingulate

Table 3. Tractography Results of Analysis Performed on the Total Group

Tract (Pyramidal)	Group (N)	Mean FA ± SD	Mean MD ± SD	p (FA)	p (MD)
Left Inferior	HC (36)	0.61 ± 0.024	0.00040 ± 0.000016	0.95	0.05
	P (36)	0.61 ± 0.029	0.00039 ± 0.000013		
Right Inferior	HC (39)	0.61 ± 0.022	0.00039 ± 0.000015	0.22	0.92
	P (39)	0.62 ± 0.031	0.00039 ± 0.000024		
Left Middle	HC (36)	0.49 ± 0.049	0.00040 ± 0.000017	0.24	0.60
	P (36)	0.48 ± 0.065	0.00040 ± 0.000021		
Right Middle	HC (39)	0.49 ± 0.038	0.00042 ± 0.000020	0.83	0.10
	P (39)	0.49 ± 0.069	0.00041 ± 0.000024		
Left Superior	HC (36)	0.61 ± 0.024	0.00045 ± 0.00002	0.27	0.77
	P (36)	0.62 ± 0.029	0.00045 ± 0.000021		
Right Superior	HC (39)	0.62 ± 0.028	0.00045 ± 0.000022	0.93	0.89
	P (39)	0.62 ± 0.030	0.00045 ± 0.000017		

Abbreviations: FA, Fractional Anisotropy; HC, Healthy Controls; MD, Mean Diffusivity; P, Patients; SD, Standard Deviation.

Table 4. Tractography Results of Analysis Performed on the Total Group

Tract	Group (N)	Mean FA ± SD	Mean MD ± SD	p (FA)	p (MD)
Body of CC	HC (39)	0.60 ± 0.016	0.00084 ± 0.000033	0.67	0.64
	P (39)	0.60 ± 0.22	0.00084 ± 0.000052		
BS	HC (39)	0.62 ± 0.018	0.00073 ± 0.000015	0.29	0.35
	P (39)	0.62 ± 0.019	0.00073 ± 0.000020		
Uncinate Fasciculus	HC (39)	0.51 ± 0.028	0.00073 ± 0.000027	0.11	0.95
	P (39)	0.52 ± 0.031	0.00073 ± 0.000045		
Cingulum	HC (39)	0.57 ± 0.024	0.00072 ± 0.000023	0.84	0.21
	P (39)	0.57 ± 0.031	0.00071 ± 0.000038		
Fornix	HC (38)	0.47 ± 0.038	0.0013 ± 0.00013	0.17	0.06
	P (38)	0.45 ± 0.034	0.0013 ± 0.00015		
IOF Fasciculus	HC (39)	0.55 ± 0.026	0.00077 ± 0.000029	0.46	0.27
	P (39)	0.55 ± 0.030	0.00076 ± 0.000038		

Abbreviations: BS, Brainstem; CC, Corpus Callosum; FA, Fractional Anisotropy; HC, Healthy Controls; IOF, Inferior Occipitofrontal; MD, Mean Diffusivity; P, Patients; SD, Standard Deviation.

gyrus, medial lemniscus, and supplementary motor area, others showed decreased FA in the putamen, corpus callosum, ansa lenticularis, superior cerebellar peduncle, cerebellum, pre- and postcentral gyrus, and prefrontal cortex.[8,11–14]

In an ROI-based approach, the authors described a WM microstructural abnormality in dystonia patients, which was observed before, but not after, BoNT treatment. They hypothesized that the dynamic WM microstructure changes provided preliminary proof of an activity-dependent brain WM plasticity.[23] As mentioned previously, our image acquisition took place 1–2 weeks after BoNT injections.

The reasons for the discrepancies between our own and previous results are probably the small sample size in some of the studies[8,13,23–25]; the use of an ROI-based[8,11,13,14,23,24] rather than a whole-brain approach, which enhances the possibility of finding statistical differences but also increases the chance of a type II error; and the different software used for imaging processing. Whole-brain analysis may not provide the appropriate power to detect small differences, and the lack of difference may just point towards a type II error. Future studies should concentrate on WM tracts more relevant to dystonia pathophysiology such as those in the cerebellum–thalamus–cortical circuits. Power might also have been an issue in our subgroup analysis.

Our results suggest that there is no primary or major involvement of the WM in CCD. Further studies should address functional abnormalities in these areas, or more relevant pre-selected white matter tracts.

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