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Diffusion tensor imaging comparison of progressive supranuclear palsy and corticobasal syndromes

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ABSTRACT

Background: Corticobasal syndrome (CBS) and progressive supranuclear palsy syndrome (PSPS) are atypical parkinsonian syndromes that are both associated with white matter tract degeneration. However, little is known about how patterns of degeneration compare across these two syndromes.
Methods: Twenty-seven subjects, nine with CBS and eighteen with probable or definite PSPS (9 pathologically confirmed) were prospectively recruited and underwent 3.0 T diffusion tensor imaging. A whole-brain voxel-based analysis was performed on fractional anisotropy (FA) and mean diffusivity (MD) images to compare both groups to each other and to 50 healthy controls.
Results: The two syndromes showed overlapping regions of reduced FA and increased MD in the body of the corpus callosum, middle cingulum bundle, and premotor and prefrontal white matter, with reduced FA also observed in the superior cerebellar peduncles in both syndromes. However, CBS showed a more supratentorial and posterior pattern of degeneration with greater involvement of the splenium of the corpus callosum, premotor, motor and parietal lobes than PSPS. Findings in CBS were also highly asymmetric. Conversely, PSPS showed a more symmetric and infratentorial pattern of degeneration, with greater involvement of the superior cerebellar peduncles and midbrain than CBS.
Conclusions: CBS and PSPS are both associated with striking white matter tract degeneration. Despite differences in the supratentorial and infratentorial distribution of degeneration, and in asymmetry, both tend to target a common structural network. Measurements of white matter tract diffusion could therefore be useful disease biomarkers in both of these syndromes.

1. Introduction

Corticobasal syndrome (CBS) and progressive supranuclear palsy syndrome (PSPS) are clinically distinguishable atypical parkinsonian syndromes. The CBS is an asymmetric syndrome characterized by ideomotor apraxia, myoclonus and extrapyramidal features, such as rigidity and dystonia [1,2], while PSPS is characterized by postural instability, vertical supranuclear gaze palsy and falls [3]. White matter damage has been associated with both PSPS and CBS [4,5], although degeneration of specific white matter tracts can now be measured using diffusion tensor imaging (DTI) which assesses the directional diffusion of water molecules. We and others have used DTI to show degeneration of the dentatorubrothalamic white matter tract, including the superior cerebellar peduncles, in PSPS [6–9]. White matter tract degeneration also appears to be a feature of CBS, with degeneration occurring in frontoparietal white matter tracts [10,11]. However, no DTI studies have directly compared white matter tract degeneration across the entire brain in PSPS and CBS, and hence it is unclear to what extent patterns of degeneration differ or overlap between these two parkinsonian syndromes. Characterizing the patterns of white matter tract degeneration typical of these two clinical syndromes will be important to determine whether DTI measurements could be useful to help diagnose subjects in which the diagnosis is equivocal. In addition, understanding breakdowns in structural connectivity in these syndromes will also shed light on network level degeneration and structure–function relationships in these syndromes [6,12,13].

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The aim of this study was therefore to use DTI to compare patterns of white matter tract degeneration in subjects with CBS or PSPS.

2. Methods

2.1. Subjects

Nine subjects meeting clinical diagnostic criteria for CBS [1] were consecutively recruited from the Department of Neurology, Mayo Clinic Rochester between June 1st 2011 and April 1st 2012. All subjects underwent a detailed clinical examination by a Movement Disorders and Behavioral Neurology Specialist (KAJ). Two of the nine subjects had undergone a Pittsburgh Compound B (PiB) PET scan and did not show amyloid deposition and one subject had abeta/tau CSF analysis and showed a profile inconsistent with Alzheimer's disease. These nine subjects were matched by age and gender to 18 subjects meeting clinical diagnostic criteria for probable PSPS [3] that had also been recruited from the Department of Neurology, Mayo Clinic, Rochester, and were evaluated by the same Movement Disorders specialist (KAJ). Of the 18 subjects with PSPS, nine have since come to autopsy and all nine have been given a pathological diagnosis of PSP [14]. No CBS subject met criteria for PSPS and no PSPS subject met criteria for CBS. This study was approved by the Mayo Clinic IRB and informed consent was obtained from all patients for participation in the study.

All CBS and PSPS subjects underwent testing on the Mini-Mental State Examination (MMSE) [15], Frontal Assessment Battery (FAB) [16], and the Movement Disorders Society Sponsored Unified Parksinon's Disease Rating Scale (UPDRS) part III [17]. Ideomotor apraxia was measured using the apraxia subscore of the Western Aphasia Battery [18]. Eye saccades were graded using a 5-point scale completed using clinical impression (The PSP Saccadic Impairment scale (PSIS) [7]).

Fifty healthy control subjects that were age and gender-matched to the CBS and PSPS subjects were also prospectively recruited. All controls performed within normal limits on standardized neurological and neuropsychological testing and had undergone the same MRI acquisition protocol as the CBS and PSPS subjects.

2.2. MRI acquisition

All subjects in the study underwent an identical 3T MRI acquisition protocol on a GE scanner that included a DTI sequence. The DTI acquisition consisted of a single-shot echo-planar (EPI) pulse sequence in the axial plane, with TR = 10,200 ms; in-plane matrix 128/128; FOV 35 cm; phase FOV 0.66; 42 diffusion encoding steps and four non-diffusion weighted b0 T2 images; slice thickness 2.7 mm (2.7 m isotropic resolution). Parallel imaging with a SENSE factor of two was used.

2.3. DTI processing

Each of the 42 diffusion-weighted images was registered to the non-diffusion weighted b0 volumes using affine transformations to minimize distortions due to eddy currents. Images were brain-extracted and fractional anisotropy (FA) and mean diffusivity (MD) maps were generated [19]. A whole-brain voxel-based analysis (VBA) was performed on both the FA and MD images to determine a set of voxels with statistically significant intensity differences across groups. In brief, FA and MD images of all subjects were nonlinearly coregistered via an iterative, groupwise registration algorithm (Advanced Normalization Tools, ANTs [20]) and normalized to a 1 mm isotropic Montreal Neurological Institute (MNI)152 standard space via the FMRIB58_FA template [21]. To increase the validity of the Gaussian field assumptions used in voxel-wise parametric tests, the images were smoothed using a Gaussian kernel with 8 mm FWMH. Finally, regions of CSF and GM were removed from consideration by masking out regions where the mean FA across coregistered subject images was below 0.2.

2.4. Asymmetry correction in CBS

Since CBS is asymmetric, whereby the greatest degeneration could be present in either left or right hemisphere, each FA and MD map was flipped in the 'x' dimension so that the more severely affected hemisphere was always positioned on the left side of the image in all CBS subjects. The most severely involved hemisphere for each subject was designated as contralateral to the most affected limb using clinical features at time of MRI, without reference to imaging. This allowed us to assess degeneration in the "more involved" and "less involved" hemispheres in CBS.

2.5. Statistical analyses

SPM5 was used to analyze the smoothed FA and MD images at the voxel-level [22]. A full-factorial model was used to compare CBS and PSPS to controls, assessed after correction for multiple comparisons using the false discovery rate (FDR) correction at $p < 0.005$. An inclusive masking analysis was performed in order to identify regions of degeneration that were common to both CBS and PSPS when compared to controls. Results of the masking analysis were assessed after correction for multiple comparisons using FDR at $p < 0.005$. In addition, statistical analyses directly comparing the CBS and PSPS groups were performed and assessed at $p < 0.001$ uncorrected for multiple comparisons. All analyses were performed separately using the FA and MD images. Age and gender were included in all analyses as covariates.

Subject demographics and clinical data were compared across groups using Wilcoxon Rank Sum tests for continuous data and Chi-squared tests for categorical data. Statistical analyses were performed utilizing the JMP computer software (JMP Software, version 8.0; SAS Institute Inc., Cary, NC) with α set at 0.05.

3. Results

3.1. Subject demographics

The CBS and PSPS groups were well matched for age, gender, and disease duration, and also showed comparable performance on the MMSE, FAB and UPDRS part III (Table 1). As expected, the PSPS subjects performed worse on the PSIS than the CBS subjects, and the CBS subjects showed worse ideomotor apraxia than the PSPS subjects.

3.2. White matter tract degeneration in CBS versus controls

The most striking regions of reduced FA and increased MD in the CBS subjects were observed in supratentorial regions, including the body of the corpus callosum, white matter of the premotor, prefrontal and motor cortices and middle cingulate bundle, compared to controls (Fig. 1 and Table 2). These abnormalities in both FA and MD were asymmetric, with greater involvement in the more involved hemisphere. Additional regions of reduced FA and increased MD were observed in the parietal lobes and fornix, and the splenium of the corpus callosum in the more involved hemisphere, and reduced FA was observed in the pons and cerebellum of both the more and less involved hemisphere, and the superior cerebellar peduncle of the less involved hemisphere (Fig. 1 and Table 2). Increased MD was also observed in the thalamus and posterior temporal white matter in the more involved hemisphere.

3.3. White matter tract degeneration in PSPS versus controls

In contrast to CBS, the most striking regions of reduced FA and increased MD in the PSPS subjects were observed in infratentorial brain regions, including the bilateral superior cerebellar peduncles and midbrain, compared to controls (Fig. 1 and Table 2). Reduced FA was also observed bilaterally in the body of the corpus callosum, middle cingulate bundle, pons, fornix and in the white matter of the premotor and prefrontal cortices (Fig. 1 and Table 2). Increased MD

Table 1
Subject demographics of the CBS and PSPS subjects and healthy controls.

	Controls	CBS	PSPS	*p* Value CBS versus PSPS
N	50	9	18	NA
Gender (% female)	16 (32%)	2 (22%)	5 (28%)	0.76
Age at MRI (years)	67.1 ± 6.8	66.8 ± 5.3	65.7 ± 6.3	0.76
Age at onset (years)	NA	63.4 ± 5.4	62.5 ± 6.4	0.80
Disease duration (years)	NA	3.3 ± 1.3	3.1 ± 1.2	0.81
MMSE (/30)	28.6 ± 0.9	27.3 ± 2.1	26.7 ± 3.4	0.96[a]
FAB (/18)	NA	12.3 ± 3.6	13.2 ± 2.3	0.65
PSIS (/5)	NA	0.3 ± 0.5	2.9 ± 0.7	<0.0001
WAB apraxia (/60)	NA	49.0 ± 7.5	59.5 ± 0.7	0.04
UPDRS part III	NA	38.3 ± 15.2	40.9 ± 16.8	0.60

Data shown as mean ± standard deviation. MMSE = Mini-Mental State Examination; FAB = Frontal Assessment Battery; PSIS = PSP Saccadic Impairment Scale; UPDRS = Unified Parkinson's Disease Rating Scale.
[a]Significant difference across all three groups $p = 0.05$.