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Diagnostic potential of dentatorubrothalamic tract analysis in progressive supranuclear palsy

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ABSTRACT

Background: The differentiation of progressive supranuclear palsy-parkinsonism (PSP-P) from Parkinson's disease (PD) remains a major clinical challenge.
Objectives: To evaluate the diagnostic potential of observer-independent assessments of microstructural integrity within infratentorial brain regions to differentiate PSP-Richardson's syndrome (PSP-RS), PSP-P and PD.
Methods: 3T MRI parameters of mean diffusivity, fractional anisotropy, grey and white matter volumes from patients with PSP-RS (n = 12), PSP-P (n = 12) and mean disease duration of 2.4 ± 1.7 years were compared with PD patients (n = 20) and healthy controls (n = 23) by using statistical parametric mapping and the spatially unbiased infratentorial template. Subsequently MRI measurements of the dentatorubrothalamic tract were determined observer-independently by a validated probabilistic infratentorial atlas. The impairment of gait and postural stability was evaluated by a sum-score derived from the Unified Parkinson Disease Rating Scale.
Results: Significant mean diffusivity increases, fractional anisotropy decreases and corresponding volume loss were localized in mesencephalic tegmentum, superior cerebellar peduncle, decussation of superior cerebellar peduncle and dentate nucleus in PSP-RS and PSP-P compared to PD and healthy controls. Altered microstructural integrity of the dentatorubrothalamic tract in PSP-RS was significantly more pronounced compared to PSP-P and correlated significantly with the gait and postural stability sum-score. Linear discriminant analysis identified diffusion tensor imaging measures of the dentatorubrothalamic tract and the gait and postural stability sum-score to classify correctly 95.5% of PRP-RS, PSP-P and PD patients.
Conclusions: Observer-independent analysis of microstructural integrity within the dentatorubrothalamic tract in combination with assessments of gait and postural stability differentiate PSP-P from PSP-RS and PD in early to moderately advanced stages.

1. Introduction

Progressive supranuclear palsy (PSP) is a neurodegenerative disorder pathologically defined by the accumulation of tau protein and neuropil threads mainly in the pallidum, subthalamic nucleus, red nucleus, pontine tegmentum, substantia nigra and dentate nucleus [1–3]. The current operational clinical diagnostic criteria of PSP require the clinical features of supranuclear gaze palsy or slowed vertical saccades and frequent falls in the first year of disease due to postural instability and this clinical presentation has been referred to as Richardson's syndrome (PSP-RS) [4,5]. However, sensitivity of the criteria is low due to the delayed evolution or even the absence of those signs in a substantial proportion of patients [5–8]. Based on a clinico-pathological series of 103 PSP cases,

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Williams and colleagues were able to delineate a distinct PSP phenotype with prominent parkinsonian features, with moderate initial therapeutic response to levodopa and absence of gaze palsy or falls within the first two years of the disease and suggested the term PSP-parkinsonism (PSP-P) [5]. Since then, the clinical spectrum of PSP presentations has enlarged further [8] and novel diagnostic criteria for PSP have been suggested to reflect this phenotypic diversity [9].

Nonetheless, the differentiation of PSP-P from Parkinson's disease (PD) patients remains a major clinical challenge [10]. Recently, MRI studies applying advanced volumetric and diffusion tensor imaging analysis revealed significant signal alterations in the midbrain, superior cerebellar peduncle (SCP), the corpus callosum and the internal capsules of PSP-RS compared to PSP-P and PD on the group level and thus hold promise as diagnostic tools [11–13]. However, there have been few attempts to distinguish among those entities on the single subject level using MRI in early disease stages [14,15].

By applying dedicated voxel-based analysis to the infratentorial brain area, the present study was conducted first to characterize objectively assessable MRI markers of mean diffusivity and fractional anisotropy in early to moderately advanced disease stages of PSP-RS, PSP-P and PD [16,17]. Secondly, derived from the results obtained at the group level, MRI metrics of the dentatorubrothalamic tract (DRTT) were investigated by using a validated probabilistic infratentorial atlas upon its potential to differentiate PSP-RS, PSP-P and PD on the individual level.

2. Methods

2.1. Subjects

Twelve patients with PSP-RS, 12 patients with PSP-P and 26 patients with PD were recruited consecutively at our centre. MRI was performed within 1 month of the initial clinical examination. To be eligible, participants had to fulfill consensus operational criteria of probable PSP and PD made by two movement disorders specialists at clinical follow-up of at least 24 months [4,18–20]. When falls, supranuclear gaze palsy, abnormal vertical saccadic eye movements and cognitive decline were the predominant clinical features in the first two years of the disease, patients were classified as PSP-RS [5,19]. In contrast, patients presenting with asymmetric bradykinesia, rigidity, or tremor and a positive response to L-dopa and no evidence of prominent postural instability with falls, supranuclear gaze palsy or abnormal vertical saccadic eye movements in the first two years, were classified as PSP-P. Further inclusion criteria, all anchored at the time of MRI, included disease duration of less than 6 years and age of 50–75 years. Motor disability was assessed in all patients in OFF drug states using part III of the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr stage. To evaluate the severity of postural instability and gait disturbance, a sum of the following items from the UPDRS part II and III was calculated (UPDRS gait and postural stability sum-score); II13 (Falling), II15 (Walking), III29 (Gait) and III30 (Postural stability). 20 out of 26 consecutively recruited PD patients were matched for gender, age and disease duration. Twenty-three healthy individuals with no signs of central nervous system disorders and a Mini-Mental State Examination score of >28 served as age and gender-matched control group. Participants with white matter lesion of grade 2 and 3 in Fazekas scale [21], space-occupying lesions, or motion artefacts were excluded. Fazekas scale quantifies the severity of white matter hyperintensity lesions on MR images, which are usually attributed to chronic small vessel ischemia. Grade 2 corresponds to larger white matter lesions that are beginning to become confluent and grade 3 corresponds to large confluent lesions. The study was approved by the Ethics Committee of the Medical University of Innsbruck. The subjects' written informed consent was obtained according to the Declaration of Helsinki.

2.2. MRI data acquisition

All MRI measurements were performed on a 3.0 T whole-body MR scanner (MagnetomVerio, Siemens, Erlangen, Germany) equipped with a twelve-channel head coil. All participants underwent the same MRI protocol, including whole-brain T1-weighted, fluid-attenuated inversion-recovery, T2 and proton density-weighted as well as diffusion tensor imaging (DTI). The MRI parameters for the coronal T1-weighted 3D magnetization prepared rapid gradient echo (3D-MPRAGE) were TR 1800 ms; TE 2.18 ms; inversion time, 900 ms; slice thickness, 1.2 mm; matrix, 256×204 pixels; number of excitations, 1; flip angle, 9°; field of view, 220×165 mm. The DTI data were acquired using spin-echo echo-planar imaging (echo time/repetition time = 83/8200 ms, bandwidth = 1596 Hz/pixel; matrix size 116×116; 45 axial slices; voxel size, $2 \times 2 \times 3$ mm^3) with 20 diffusion gradient directions with a b-value of 1000 s/mm^2 and one reference image with b = 0.

2.3. Imaging post processing

To avoid a priori assumptions through region of interest (ROI) analysis on brain areas of potential interests, we applied a voxel-based analysis of entire infrantentorial region to multimodal mean diffusivity (MD), fractional anisotropy (FA) and volumetric measures of the grey and white matter compartments [16,17]. Grey and white matter volume, MD and FA measures were subjected to statistical parametric mapping (SPM, Wellcome Department of Cognitive Neurology, London, UK [16]). The software package SPM12 implemented in Matlab 7.8 (Mathsworks Inc., Sherborn, MA) was used to preprocess and analyze MRI data. The infratentorial structures (i.e., the cerebellum and brainstem) were isolated from the supratentorial structures on the MPRAGE images and the segmented grey matter (GM) and white matter (WM) images were generated using the SUIT toolbox v2.7 [17]. The cropped images were then normalized onto the spatially unbiased high-resolution infratentorial template (SUIT), and the resulting transformation parameters were applied to the segmented volumetric images. A modulation of the segmentation map using the Jacobian determinants was undertaken to compensate for volume changes during the normalization. The deformation map generated in the normalization step was also applied to the previously coregistered MD and FA images. Finally, the normalized infratentorial images were smoothed with a 4-mm full-width half-maximum Gaussian kernel in order to accommodate inter-individual anatomic variability and to improve signal to noise ratios for the statistical analysis. A masking threshold of 10% of the lower image signal was applied to reduce signal noise. For DTI analysis, age was included as a covariate. For voxel based morphometry, age and total intracranial volume were entered as covariates. Subsequently a previously validated automated, atlas-based ROI analysis of the infratentorial brain region including the DRTT and pontocerebellar tract (PCT), which is independent from our categorical SPM analysis, was evaluated upon its applicability in clinical practice [22]. Observer-independently defined ROI's were transformed to individual subject's space using the deformation parameters obtained from the normalization step. Individual subject's volume and DTI metrics of the DRTT and PCT were extracted, adjusted for total intracranial volume and correlated to demographic and clinical parameters including semiquantitative assessments of gait and postural stability. Supplementary Fig. 1 shows a sample of the ROIs of the DRTT