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Clinical and cognitive correlations of regional gray matter atrophy in progressive supranuclear palsy

Alfonso Giordano [a,b,1], Alessandro Tessitore [a,*,1], Daniele Corbo [a], Giovanni Cirillo [a], Rosa de Micco [a], Antonio Russo [a,b], Sara Liguori [a], Mario Cirillo [c], Fabrizio Esposito [d,e], Gioacchino Tedeschi [a]

[a] Department of Neurology, Second University of Naples, Piazza Miraglia, 2, 80100 Naples, Italy
[b] IDC Hermitage Capodimonte, Naples, Italy
[c] Neuroradiology Service, Second University of Naples, Italy
[d] Department of Neuroscience, University of Naples Federico II, Italy
[e] Department of Cognitive Neuroscience, Maastricht University, Maastricht, The Netherlands

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ABSTRACT

Background: Progressive supranuclear palsy is the most common neurodegenerative bradykinetic-rigid syndrome after Parkinson's disease. Several volumetric studies have revealed a widespread cortical and subcortical gray matter atrophy, however the correlations between the pattern of gray matter loss and clinical-cognitive features have been poorly investigated.
Methods: By using 3-T magnetic-resonance imaging and voxel-based morphometry we compared gray matter volume in 15 patients with progressive supranuclear palsy, 15 patients with Parkinson's disease and 15 healthy controls. All patients underwent a clinical and neuropsychological evaluation.
Results: In agreement with previous studies, patients with progressive supranuclear palsy, compared to patients with Parkinson's disease and healthy controls, showed a reduced gray matter volume in several cortical and subcortical areas including cerebellum, frontal, temporal and parahippocampal cortical structures. We did not find any significant gray matter volume changes when comparing patients with Parkinson's disease vs healthy controls. Among different significant correlations between motor-cognitive features and gray matter loss, we detected a significant correlation between fronto-cerebellar gray matter atrophy and executive cognitive impairment in patients with progressive supranuclear palsy.
Conclusions: Our findings confirm that gray matter loss in patients with progressive supranuclear palsy involves several brain areas and suggest that cerebellar atrophy may play a role in the pathogenesis of cognitive dysfunction in patients with progressive supranuclear palsy due to a disruption of its modulation on executive functions.

1. Introduction

Progressive supranuclear palsy (PSP) is the most common neurodegenerative bradykinetic-rigid syndrome after Parkinson's disease (PD) and it is characterized by motor and cognitive deficits [1]. Although several clinical variants have been recently identified, differing in severity, preferred regions of detectable pathology and clinical features, Richardson's syndrome remains the most frequent form clinically characterized by postural instability, supranuclear gaze palsy, progressive axial rigidity and bulbar palsy as well as cognitive impairment even at the earliest stages [2]. In patients with PSP usually attention and executive functions (EF) are compromised and deficits in both verbal and non-verbal memory have been reported, while a relative preservation of recognition has been found [3]. In particular patients' performance to frontal assessment battery (FAB) and phonological verbal fluency (pVF) tests has been shown to be significantly impaired, confirming the value of these tests in detecting early cognitive impairment in patients with PSP [3]. Several volumetric studies have revealed a widespread cortical and subcortical gray matter (GM) atrophy in patients with PSP involving frontal and temporal cortices, brainstem and basal ganglia [4,5]. Moreover, cerebellar atrophy in PSP has been reported both *in-vivo* [6,7] and post-mortem studies [8].

Clinical and cognitive correlations with structural changes, as assessed by advanced magnetic-resonance imaging (MRI)

* Corresponding author. Tel.: +39 0815665299; fax: +39 0815665095.
E-mail address: alessandro.tessitore@unina2.it (A. Tessitore).
[1] These authors equally contributed to this work.

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techniques, have been already investigated in PSP. Previous reports [9,10] have shown that motor impairment was correlated with smaller volume of midbrain, caudate nucleus and motor cingulate cortex whereas a reduced frontal volume in PSP was associated with poorer performance on tests exploring EF. However, based on several brain regions involvement, we hypothesize that cognitive impairment in PSP may arise, at least in part, as a consequence of damage to other cortical and subcortical pathways [11]. Therefore, the aims of the present study are: 1) to explore the pattern of GM tissue loss in patients with PSP compared to patients with PD and healthy controls (HCs); 2) to investigate the correlations between GM atrophy and clinical-cognitive features of patients with PSP.

2. Methods

2.1. Patients population

Fifteen patients with PSP and 15 patients with PD according respectively to National Institute of Neurological Disorders and Stroke (NINDS) and the Society for PSP criteria [12] and to the clinical diagnostic criteria of the United Kingdom Parkinson's disease Society Brain Bank for idiopathic PD [13] were included in the study. Inclusion criteria for patients with PD were: age of 45 years or older; disease duration more than 5 years; a prolonged and sustained response to levodopa. Exclusion criteria for PD were: dementia according to clinical diagnostic criteria for dementia associated with PD [14]; major depression according to DSM-IV criteria for current major depression [15] and clinically significant comorbidities including cardiovascular or cerebrovascular disease.

Inclusion criteria for patients with PSP were: clinically probable diagnosis according to the NINDS criteria [12]; magnetic-resonance parkinsonism index (MRPI) greater than 13.55 [16], while lack of or poor response to levodopa was considered an adjunctive inclusion criterion.

A group of 15 age- and sex-matched HCs with no previous neurological or psychiatric diseases and with normal brain MRI was also recruited.

All participants gave written informed consent to take part into the study, which was approved by the local Ethical Committee.

2.2. Clinical, motor and neuropsychological assessment analysis

All patients underwent clinical and cognitive evaluation aimed at exploring mainly the EF. We recorded demographic data, disease history and administered the UPDRS [17]; the Mini Mental Status Examination (MMSE) for a general cognitive evaluation; the Frontal Assessment Battery (FAB), to assess frontal lobe functions; the Phonological Verbal Fluency (pVF) to estimate mental flexibility; the ten point clock test (TPCT) for visuospatial abilities and the Beck Depression Inventory Scale (BDI) to detect depressive symptoms. Test scores were corrected for current normative values. The commonly accepted Postural Instability Gait Disturbance sub-score (PIGDs) [18] was calculated in both patients' groups by adding items 13, 14, 15, 29 and 30 from the motor and activities of daily living of the UPDRS which comprises historical questions related to falling, freezing, walking, gait and postural stability, respectively. Motor and cognitive functions were evaluated by two different raters. An experienced neurologist performed the motor examination; neuropsychological tests were administered by a trained neuropsychologist blinded to clinical diagnosis.

2.3. Imaging parameters

The thirty patients with PSP and PD and 15 matched HCs underwent volumetric MRI brain scanning. Magnetic-resonance images were acquired on a 3T GE Medical System scanner equipped with an 8-channel parallel head coil. Structural MRI data were acquired using a 3D T1-weighted sagittal images (GE sequence IR-FSPGR, TR = 6988 ms, TI = 1100 ms, TE = 3.9 ms, flip angle = 10°, voxel size = 1 × 1 × 1.2 mm^3). Gross anatomical abnormalities were ruled out by an experienced neuroradiologist who evaluated MRI scans for each subject.

2.4. Statistical analysis of clinical, motor and neuropsychological data

Demographic and clinical features of patients with PSP or PD were compared by the *t*-test for independent samples or Fisher's exact test, as appropriate.

Given the small number of subjects in each group and to avoid type 1 errors, between group comparisons on cognitive measures were evaluated by non-parametric analysis, namely, the Mann–Whitney *U* test. Computation was supported by the Statistical Package for the Social Sciences (SPSS 16.0) software. Significance threshold was set to $p \leq 0.05$.

2.5. Voxel-based morphometry (VBM)

Data were processed and examined by SPM8 software (http://www.fil.ion.ucl.ac.uk/spm), where we applied VBM implemented in the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html) with default parameters incorporating the DARTEL toolbox in SPM8. This was used to obtain a high-dimensional normalization protocol [19]. Images were bias-corrected, tissue-classified, and registered by using linear (12-parameter affine) and nonlinear transformations (warping) within a unified model [19]. Subsequently, the warped GM segments were affine-transformed into Montreal Neurological Institute (MNI) space and were scaled by the Jacobian determinants of the deformations to account for the local compression and stretching that occurs as a consequence of the warping and affine transformation (modulated GM volumes) [19]. Finally, the modulated volumes were smoothed with a Gaussian kernel of 8-mm full width at half maximum. The GM volume maps were statistically analyzed by using the general linear model based on Gaussian random field theory. Statistical analysis consisted of an analysis of covariance (ANCOVA) with total intracranial volume (TIV) and age as covariates of no interest. For each group, we defined linear contrasts (1 as group of interest; −1 as a comparing group; 0 as group of non interest) to test for differences in GM volumes between the groups: 1) each group vs HCs (patients with PSP vs HCs: [1 0 −1]; patients with PD vs HCs: [1 −1 0]); 2) each group vs the other (patients with PSP vs patients with PD [1 −1 0]; patients with PD vs patients with PSP [−1 1 0]). GM differences between groups were assessed using significance level of $p \leq 0.05$, FWE-corrected for multiple comparisons. The results were also assessed at an uncorrected statistical threshold of $p < 0.001$. Only clusters comprising 100 or more voxels were reported. To correlate GM volume changes and clinical and neuropsychological data, we performed a correlation analysis by using the multiple regression function of SPM8. Correlation analyzes were performed inside and outside specific regions of interest (ROIs). We considered ROIs to be the identified regions that showed the most significant GM change in the comparisons between groups. The resulting ROI was transformed into a binary mask that was applied explicitly to compute regression analysis. Correlation results were assessed at an uncorrected threshold of $p < 0.001$.

The coordinates of voxels exhibiting the greatest group effects were transferred from MNI space to Talairach space by using M. Brett's transformation (http://www.mrccbu.cam.ac.uk/Imaging/contents.html).

3. Results

3.1. Clinical and neuropsychological findings

The demographic, clinical data, cognitive features and MRI parameters of patients with PSP and PD compared with HCs are shown in Table 1. No significant differences were observed between patients with PSP and patients with PD in age, gender and handedness, whereas disease duration was significantly longer in patients with PD. As expected H&Y stage, UPDRS motor score and PIGDs were significantly higher in the PSP group compared to patients with PD. Moreover, patients with PSP performed significantly worse than patients with PD on cognitive tests, exhibiting lower scores on MMSE, FAB, pVF and TPCT.

3.2. VBM

The analysis of regional volume differences revealed that all patients with PD showed no significant GM differences when compared to HCs. However, significant GM volume differences, involving both supra and infratentorial structures bilaterally, were detected when PSP and HCs were compared. In particular, patients with PSP showed reduced GM volume in several clusters including left cerebellum (anterior lobe), right cerebellum (posterior lobe), left (inferior, middle and superior) frontal gyrus, right (superior and inferior) and left middle temporal gyrus, right and left parahippocampal gyrus and left subcallosal gyrus. Moreover, GM volume differences were found in left cerebellum (anterior lobe), left parahippocampal gyrus and left middle frontal gyrus when patients with PSP were compared to patients with PD (see Table 2 and Fig. 1 for further details on Talairach coordinates and statistical significance).

3.3. Correlation analyzes

In patients with PSP a significant positive correlation was detected between FAB score and GM volume in left superior frontal