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<Short Communications>**Pallidal dopaminergic denervation and rest tremor in early Parkinson's disease: PPMI cohort analysis**

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Running head: Globus pallidus dopamine and rest tremor in PD

Key Words: Rest tremor; Globus pallidus; Dopamine transporter; SPECT; Parkinson's disease

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ABSTRACT

Backgrounds: Over recent years there have been some conflicting reports upon the role of pallidal dopaminergic denervation in rest tremor in Parkinson's disease.

Objectives: To clarify this issue we analyzed the clinical and 123I-FP-CIT SPECT data of a large cohort of early Parkinson's disease patients enrolled in the PPMI study.

Methods: Pallidal and striatal dopamine transporter uptake ratios were calculated in 382 patients (120 no-tremor, 60 tremor-dominant, and 202 indeterminate) and 150 controls. A region of interest (ROI) approach was used to estimate DAT uptake ratios from 123I-FP-CIT SPECT scans in the caudate nucleus, putamen, and globus pallidus after normalization to a DAT template. DAT uptake ratios for each region were compared between subgroups using ANCOVA and linear regression analyses were performed to evaluate the relationship between severity of rest tremor and regional DAT uptake ratios.

Results: PD patients had significantly lower DAT uptake ratios in the pallidum, putamen and caudate as compared to healthy controls ($p < 0.001$). ANCOVA showed inter-PD subgroup differences in DAT uptake ratios in the putamen and pallidum ($p < 0.05$) after adjustment for age and disease duration, with post-hoc comparisons revealing significantly higher DAT uptake ratios for the tremor-dominant subgroup as compared to non-tremor and indeterminate subgroups ($p < 0.016$). There was no significant relationship between rest tremor severity and pallidal DAT either in the tremor-dominant subgroup or in the total PD population.

Conclusions: Pallidal dopaminergic denervation appears unrelated to rest tremor severity in early Parkinson's disease.

INTRODUCTION

The pathophysiology of rest tremor in Parkinson's disease (PD) has not been completely understood and several hypotheses are still in debate. Dopaminergic denervation in the basal ganglia is considered to be a prerequisite condition but likely constitutes only part of the explanation.[1] This is highlighted by several imaging studies reporting no correlation between striatal denervation and severity of resting tremor in PD.[2-5]

The recently proposed 'dimmer-switch model'[6] provides a possible explanation for the complex action of dopamine on rest tremor through an interplay between dopaminergic denervation of the globus pallidus (GP), which can be thought of as the trigger, and the activity of cerebello-thalamo-cortical circuit, which is responsible for modulating tremor severity and amplitude.[5] Critically, this model assumes that pallidal dopaminergic denervation be more pronounced in tremor-dominant than in akinesia/rigidity-dominant patients. However, whether such dopaminergic denervation is associated with rest tremor in PD is still controversial. While one study demonstrated a correlation between GP dopamine transporter (DAT) reduction and rest tremor[5], another study found no difference in pallidal DAT loss between patients with bilateral, unilateral, or without tremor.[7] It should be noted that these studies only included a small number of patients without controlling dopaminergic medication effect, thus limiting conclusiveness.

The current study aims to investigate whether pallidal dopaminergic denervation is related to resting tremor severity in a large prospective cohort of early untreated PD patients.

METHODS

Study design and participants

PD patients and healthy controls (HC) who enrolled in the Parkinson's Progression Marker Initiative (PPMI) study and received screening ^{123}I -FP-CIT SPECT were eligible. PD patients were within 2 years of diagnosis and in anti-parkinsonian drug-naïve state at the time of scanning. Reconstructed and attenuation corrected ^{123}I -FP-CIT SPECT images were downloaded for 430 PD and 193 HC on 8th September 2016 from the PPMI database (<http://www.ppmi-info.org/data>). Clinical data described below were also downloaded on the same date.

Patient Classification

Clinical information including demographics, medication history, duration of PD, and scores for the Movement Disorders Society revised Unified PD Rating Scale (MDS-UPDRS) assessed at baseline were acquired from the PPMI database. Rest tremor severity index was calculated based on the MDS-UPDRS part-III, defined as the product of the total rest tremor amplitude score (item 3.17) in the most affected side and constancy score (item 3.18). PD patients were classified into three subgroups; tremor-dominant, no-tremor and indeterminate. Tremor-dominant was defined if patients had a rest tremor severity index ≥ 2 ; rigidity score ≤ 1 (item 3.3); body bradykinesia score ≤ 1 (item 3.14). No-tremor was defined if patients had a rest tremor severity index score of zero. All other patients were classified as indeterminate.

^{123}I -FP-CIT SPECT data analysis

Image pre-processing

^{123}I -FP-CIT SPECT was performed during screening visits using standardized imaging protocols (<http://www.ppmi-info.org/data>). Downloaded ^{123}I -FP-CIT SPECT images were first rigid registered to an in-house custom DAT template created from a series of thirty-three ^{11}C -PE2I positron emission tomography scans,[8] which is a radioligand with high specificity for DAT.[9, 10] Registered ^{123}I -FP-CIT images were then spatially normalized to this DAT template using 12-parameter affine registration and non-linear warping procedure in SPM12 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, London, UK). A T1-weighted anatomical template in spatial correspondence with the DAT template[8] was then used for manual ROI delineation. We opted for this procedure to ensure anatomically accurate and consistent delineation with particular regard for discrimination within the lentiform nucleus and to reduce potential operator bias otherwise inherent in regional tracing based on SPECT voxel intensities. All normalized SPECT images were visually inspected against DAT and T1-weighted templates to ensure adequate alignment.

Region of interest analysis

Regions of interest (ROI) were manually drawn for the bilateral putamen, caudate nucleus, GP and occipital cortex on the T1-weighted template in Analyze 11.0 (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN). Hemispheric ROI volumes for the putamen, caudate, and GP were 3592mm^3 , 2760mm^3 and 1624mm^3 , respectively. The occipital cortex was used as a reference region and defined by placing a circular ROI in each hemisphere on 10 sequential slices (ROI volume = 5920mm^3) (Supplementary figure). The specific DAT binding ratio for each ROI was calculated as

in our previous paper:[11] $\text{Specific binding ratio} = \frac{\left(\frac{\text{ROI counts}}{\text{pixels}}\right) - \left(\frac{\text{occipital counts}}{\text{pixels}}\right)}{\left(\frac{\text{occipital counts}}{\text{pixels}}\right)}$

Statistical analysis

Statistical analyses were performed using IBM SPSS version 22 (Armonk, NY: IBM Corp). Differences in baseline clinical/demographic characteristics between PD subgroups were assessed using one-way analysis of variance (ANOVA) for continuous variables, Kruskal-Wallis test in cases where normality (Shapiro-Wilk <0.05) was violated and for binary variables using chi-square test. Group comparison of regional DAT uptake ratios averaged across hemispheres between PD_{All} and HC groups was conducted using independent t-tests. One-way analysis of covariance (ANCOVA), adjusting for age and followed by *post-hoc* Bonferroni comparisons was utilized to evaluate differences in DAT uptake ratios between PD subgroups for the more and less affected hemispheres separately. Associations between rest tremor (rest tremor severity index, tremor amplitude, constancy of tremor) and pallidal and putaminal DAT uptake ratios were investigated using linear regression with age as a nuisance covariate.

RESULTS

Subjects were excluded due to unavailable clinical data (23 PD, 35 HC) and poor image acquisition or failure in normalization (25 PD, 8 HC). 382 PD [PD_{All}: 134 females (35.1%), age = 61.8 ± 9.5 years] and 150 HC [51 females (34%), age = 61.2 ± 11.0 years] participants were therefore included in the final analysis. There were no significant

differences in age and sex distributions between PD_{All} and HC groups. Sixty patients were classified as tremor-dominant, 120 patients as no-tremor and 202 patients as indeterminate. Clinical comparisons between the three PD subgroups are shown in Table 1. Compared with no-tremor and indeterminate, the tremor-dominant subgroup had milder disease, showing significantly lower MDS-UPDRS scores and HY stage. Rest tremor severity index was highest in the tremor-dominant subgroup (Table 1).

Dopamine transporter uptake ratios

PD_{All} group had significantly reduced DAT uptake ratios compared to HC in all three ROIs ($p < 0.001$). Mean reductions in DAT uptake ratios for the PD_{All} group were 28.2% for caudate nucleus, 38.9% for putamen and 43.1% for GP.

When we compared DAT uptake ratios amongst PD subgroups, significant inter-subgroup differences were found in both sides of the putamen and in the less affected GP (Supplementary table). *Post-hoc* analysis revealed that the tremor-dominant subgroup had higher DAT uptake ratios in the putamen compared to the indeterminate subgroup, and in the less affected GP as compared to the no-tremor subgroup (Figure 1). No significant results were found for caudate DAT uptake ratios.

Linear regression analysis

No significant relationship was found between GP DAT uptake ratios and rest tremor severity index, tremor amplitude or constancy of rest tremor scores in the tremor-dominant PD subgroup as well as in the PD_{All} group ($p > 0.05$). This lack of association was consistently shown in both the more affected and less affected GP ($p > 0.05$). Additionally, we found no significant relationship between putaminal DAT uptake ratios

and tremor severity measures in both tremor-dominant and PD_{All} groups ($p > 0.05$).

DISCUSSION

In a large cohort of early PD patients, we found that tremor-dominant patients exhibit milder putaminal and pallidal dopaminergic denervation compared with indeterminate and no-tremor PD cases, despite differences in disease duration. Additionally, pallidal DAT availability was not predictive of rest tremor severity in this cohort.

Our findings are in agreement with those previously reported by Isaias and colleagues[7] and therefore do not support the interpretation that tremor severity is associated with more severe dopamine depletion in the pallidum, as proposed by Helmich and colleagues.[5] However, SPECT used in all these studies including ours has limited resolution for GP, so we tried to enhance accuracy and consistency in regional delineation by using corresponding DAT and T1-weighted anatomical templates in our imaging analysis pipeline, and analyzed data from a significantly large number of drug-naïve PD patients, therefore our measures were both unaffected by drug treatment and more robust than in previous reports. In line with our *in vivo* observations, one post-mortem biochemical study in eight PD and five control brains showed that dopamine loss was less severe in tremor-dominant cases compared to akinetic-rigid and classic PD types in the GP, as well as in the putamen.[12] In the present study, we clearly demonstrate a milder degree of pallidal dopaminergic denervation in tremor-dominant PD patients.

Our results however, are not necessarily in opposition to those indicating a close relationship between pallidal activity and rest tremor[5, 6] as they only reflect early

disease and tremor mechanisms may change with PD progression. It is possible that GP dysfunction may become worse over time and contribute to tremor as described by Helmich and colleagues in patients at more advanced stages than ours.[5] The underlying mechanism may just be more complex and probably involve dopaminergic and non-dopaminergic input rather than dopaminergic input alone. In the PPMI cohort, we have previously reported reductions of serotonin transporter availability in the raphe nuclei that correlated with measures of rest tremor severity.[11] Noradrenergic involvement has also been suggested, though further larger scale work is required to confirm this[7].

In conclusion, we have demonstrated a limited role of pallidal dopaminergic denervation in early parkinsonian rest tremor. We suggest that non-dopaminergic mechanisms may be of importance for the clinical feature of rest tremor in PD.

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Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org.

Author Contributions

J.Y.L.: conception and design of the study, acquisition and analysis of data, drafting the manuscript, N.P.L-K.: design of the study, analysis of data, drafting a significant portion of the manuscript; J.P.: analysis of data, critical review of the manuscript, G.D.: conception of the study, critical review of the manuscript, N.P.: conception and design of the study, interpretation of data, drafting and critical review of the manuscript, P.P.:

design of the study, interpretation of data, critical review of the manuscript

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Figure Legends

Figure 1. Comparisons of dopamine transporter uptakes in the pallidum, putamen, and caudate nucleus between the Parkinson's disease subgroups. A. DAT uptakes in the more affected hemisphere. B. DAT uptakes in the less affected hemisphere. DAT uptakes in healthy controls are plotted as a reference showing averaged values of both hemispheres. ANCOVA test results adjusting for age are presented above respective plots. In the post-hoc analysis, the tremor-dominant subgroup had higher DAT uptakes in the less affected pallidum compared with the no-tremor subgroup ($p = 0.010$, age & PD duration-adjusted), and in both more and less affected putamen compared to the indeterminate subgroup [$p = 0.011$ (A) and 0.010 (B), age & PD duration-adjusted]. DAT =dopamine transporters, HC =healthy controls, *Denotes significant pairwise comparison at $p < 0.016$.

Table 1. Baseline characteristics of the tremor-dominant, no-tremor and indeterminate PD subgroups

Supplementary Table. Comparison of DAT uptake ratios between the three PD subgroups.

Supplementary Figure. A representative picture of ROI placement on the normalized SPECT image. ROIs were manually drawn using the Analyze 11.0 (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN) on the T1-weighted anatomical template in spatial correspondence with the DAT template.

Table 1. Baseline characteristics of the tremor-dominant, no-tremor and indeterminate PD subgroups

Characteristics	Indeterminate (n =202)	No-tremor (n =120)	Tremor-dominant (n =60)	p-value
Gender, female, <i>n</i> (%)	75 (37.1)	36 (30.0)	23 (38.3)	0.366*
Age, years	62.8 ±9.0	59.1 ±9.7	63.7 ±9.6	0.001^{ac}
Duration of PD, months	7.7 ±7.6	4.8 ±4.0	6.1 ±5.8	<0.001^c
MDS-UPDRS total score	34.7 ±12.7	31.2 ±13.0	24.0 ±8.8	<0.001^{abc}
Part 1	1.2 ±1.6	1.4 ±1.6	1.0 ±1.3	0.226
Part 1 - questionnaires	4.5 ±3.0	4.3 ±3.2	3.9 ±3.7	0.514
Part 2	6.1 ±4.3	6.4 ±4.4	4.5 ±3.1	0.010^{ab}
Part 3	22.8 ±8.7	19.1 ±8.2	14.6 ±4.3	<0.001^{abc}
Hoehn & Yahr stage	1.6 ±0.5	1.6 ±0.5	1.4 ±0.5	<0.001^{ab†}
Rest tremor severity index	3.72 ±3.38	0	5.10 ±3.10	<0.001^{abc}
Amplitude of rest tremor	1.72 ±0.97	0.04 ±0.21	2.13 ±0.79	<0.001^{abc}
Consistency of rest tremor	1.86 ±1.00	0.04 ±0.20	2.35 ±0.97	<0.001^{abc}

Data are shown as mean ±standard deviation unless otherwise indicated.

PD =Parkinson's disease; MDS-UPDRS =Movement Disorders Society Task Force revised Unified Parkinson's disease rating scale. Bold style means statistical significance. Comparison was done using the ANOVA test with post-hoc analysis unless otherwise specified.

* comparison by the Chi-square test

† comparison by the Kruskal-Wallis test

^asignificant difference between the tremor-dominant vs. no-tremor subgroups, corrected $p < 0.05$

^bsignificant difference between the tremor-dominant vs. indeterminate subgroups, corrected $p < 0.05$

^csignificant difference between the no-tremor vs. indeterminate subgroups, corrected $p < 0.05$

Highlights

Tremor-dominant PD patients had relatively mild dopaminergic denervation.

Pallidal DAT density could not determine rest tremor severity in drug-naïve PD.

Nondopaminergic mechanism in the pallidum might be important for rest tremor in PD.