NeuroImage: Clinical 11 (2016) 68–72

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Relation of 18-F-Dopa PET with hypokinesia-rigidity, tremor and freezing in Parkinson's disease

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ARTICLE INFO

Article history:
Received 15 November 2015
Received in revised form 7 January 2016
Accepted 11 January 2016
Available online 12 January 2016

Keywords:
Parkinson's disease
F-Dopa PET
Hypokinesia
Rigidity
Tremor

ABSTRACT

Introduction: In this retrospective study concerning patients with Parkinson's disease (PD) scanned with 18-F-Dopa PET ($N = 129$), we looked for an association between reduced 18-F-Dopa uptake and the key PD symptoms tremor and hypokinesia-rigidity. We hypothesized to find a stronger correlation between dopaminergic depletion in the striatum and hypokinesia-rigidity compared to tremor.
Methods: The onset side of symptoms (documented for 102 patients) as well as the first registered UPDRS (available for 79 patients) was used to correlate with F-Dopa uptake values in the caudate nucleus and putamen in this large retrospective sample.
Results: Reduced F-Dopa uptake was contralateral to hypokinesia-rigidity symptoms and correlated with its severity (quantified by UPDRS). For tremor severity, no correlation was seen with F-Dopa reduction. Furthermore, freezing of gait correlated with reduced F-Dopa uptake in the putamen of the right hemisphere.
Conclusion and discussion: Our results, obtained in a large patient group, provides support for the concept that tremor in PD is not only based on a dopamine related pathway but may rely on a different pathway.

1. Introduction

Parkinson's disease (PD) is characterized by asymmetrical neuronal loss in the substantia nigra, which results in striatal dopamine depletion and contralateral symptoms. Dopamine depletion can be assessed in vivo by Position Emission Tomography (PET) using the tracer L-3,4-Dihydroxy-6-18F-fluorophenylalanine (F-Dopa), an indicator of presynaptic dopaminergic function. In this way, clinical PD characteristics can be 'neurochemically' investigated (Loane and Politis, 2011; Vingerhoets et al., 1997). Dopaminergic deficit, e.g., has been repeatedly associated with hypokinesia and rigidity (Benamer et al., 2003; Eggers et al., 2014; Spiegel et al., 2007). Such association, however, is less evident for tremor, another cardinal PD feature (Benamer et al., 2003; Isaias et al., 2007; Spiegel et al., 2007; Martin et al., 2008; Eggers et al., 2014). This generated the idea that PD tremor may not only depend on depletion of striatal dopamine but that deficit of other monoaminergic neurotransmitters such as serotonin (Doder et al., 2003) or noradrenalin (Isaias et al., 2012) may play a role. Alternatively, dopaminergic deficit in specific regions of the basal ganglia regions (pallidum) has been suggested to generate the tremor by functional interaction of this site with cerebello-thalamic circuitry (Helmich et al., 2011).

The results from these studies were based on various analysis methods, patient numbers and disease duration. Here, we investigated the association between striatum F-Dopa uptake and the main PD symptoms tremor and hypokinesia-rigidity in a large patient population, scanned at a relative early stage of disease and employing a straight forward transparent analysis method. We hypothesized to find a correlation between dopaminergic depletion and contralateral dominance of hypokinesia-rigidity, while such correlation was not expected for tremor. We further assessed the possible relation between striatum F-Dopa uptake and Freezing of gait (FOG) (Giladi et al., 2001). Pathophysiology underlying this disabling symptom remains unclear, but improvement by levodopa supports the relation with a dopaminergic state (Bartels et al., 2006).

2. Patients and methods

2.1. Study population

PD patients were retrospectively identified from the Neurology Department, University Medical Center Groningen. Over an 18 month period, we included a consecutive sample of 370 patients who visited our department with either a new or previously established diagnosis of idiopathic PD. Diagnosis was made by a movement disorders neurologist

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http://dx.doi.org/10.1016/j.nicl.2016.01.010

taking into consideration the history, examination and imaging if performed. Three patients were excluded due to change of diagnosis and one because the patient file was incomplete. This resulted in 366 patients classified as PD (57% male, age of first symptoms 58.7 years ± 11.8; mean ± SD). F-Dopa PET was performed in 129 patients at 3.2 ± 3.9 years disease duration. This scan was made to gain further support for the diagnosis PD. Within this group, either tremor ($N = 60$) or hypokinesia-rigidity ($N = 42$) was the onset symptom, while for the remaining 27 patients another or unknown onset symptom was reported. The Unified Parkinson's Disease Rating Scale (UPDRS) sub-score was described in 79 of these 129 patients (Fig. 1).

This enabled correlating type of onset symptom and F-Dopa values in 102 patients, while for 79 patients possible correlation between UPDRS sub-scores for either tremor or hypokinesia-rigidity and F-Dopa values could be assessed. Ethical committee approval was not required as this study concerned retrospective analysis of restricted parameters.

2.2. Data retrieval

General patient characteristics, according to standard medical care, were documented by the treating neurologist in the medical file. These characteristics were retrieved including year of onset and year of PD diagnosis. Onset of PD was defined as the first PD-attributed sign noticed by the patient, a relative or care provider. Onset symptom was classified as tremor, hypokinesia-rigidity or another/unknown onset type. Likewise we assessed whether experienced FOG was registered in the patient history. FOG was assessed at each clinical visit by asking whether a patient feels their feet getting glued to the floor while either walking, turning or trying to initiate walking (Giladi et al., 2000). If seen during examination (generally performed in on-state without medication stop), FOG was also recorded. We acknowledge that this documentation of FOG does not concern a highly specific assessment. We further retrieved the patients' first recorded UPDRS part III which, in general, was also assessed in on-state. Using items 20 and 21 of the UPDRS motor score (hands and feet), a sum rest tremor sub-score was created for the right and left side separately. Similarly, a sum hypokinesia-rigidity score (items 22–26) was obtained for each side. A ratio with each maximum UPDRS sub-score, subsequently expressed as percentage, was used to facilitate the comparison between rigidity and tremor. For rigidity, the maximum sub-score was 24 points while it was maximally 8 points for tremor, thus allowing between-group comparisons.

By reviewing radiology reports of clinically obtained PET scans, we extracted F-Dopa uptake values for standard regions of interest in putamen and caudate nucleus, both contra- and ipsilateral to the dominant symptom side. Striatum F-Dopa uptake was expressed as a ratio relative to occipital reference tissue.

2.3. Statistical analysis

General characteristics of patients with and without a F-Dopa PET were compared using a Mann–Whitney U-test for continuous non-

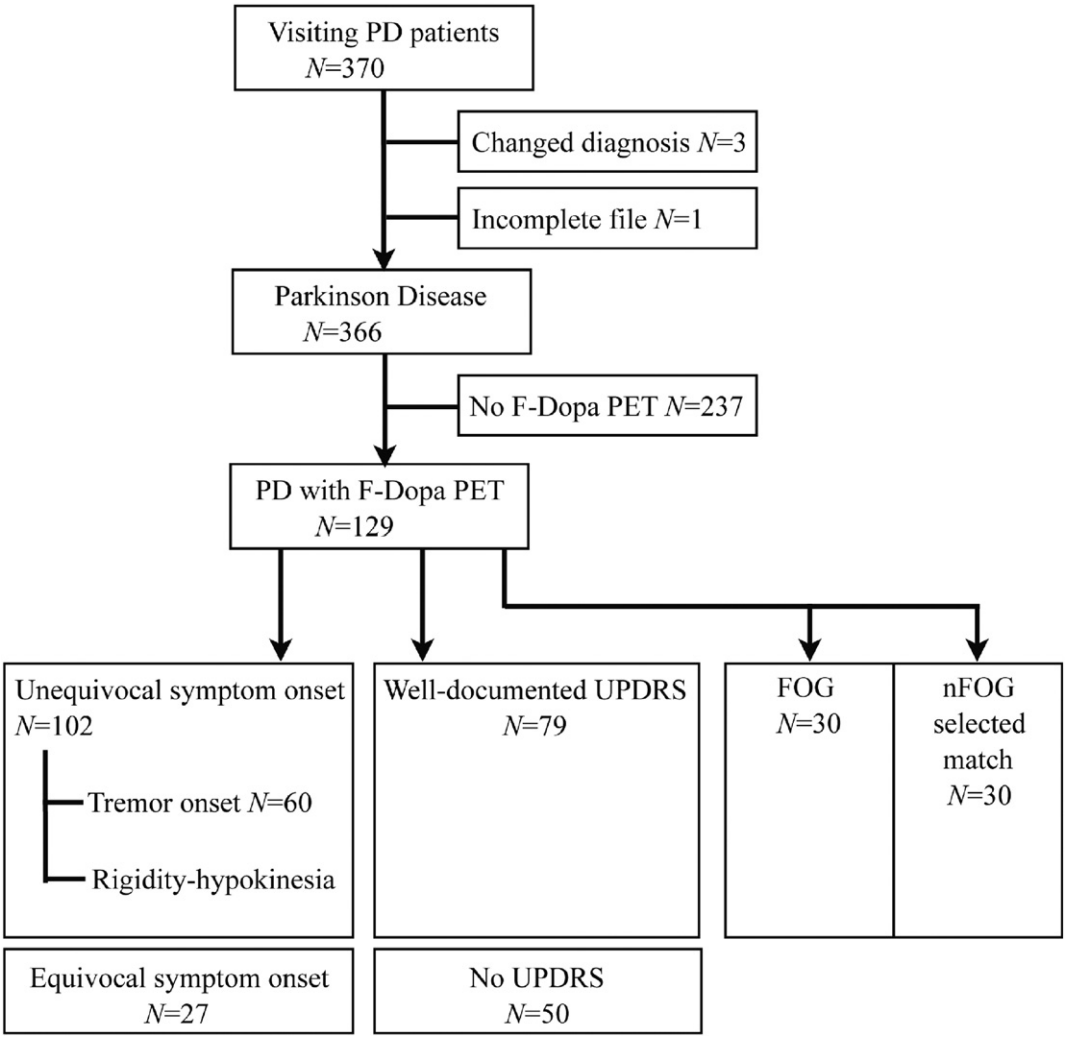

Fig. 1. The flow diagram showed the distributions of PD patients.

Gaussian data and a chi-square test for binary data. The onset symptom type, first obtained UPDRS tremor and UPDRS hypokinesia-rigidity subscores were correlated with F-Dopa uptake values by Spearman correlations.

Thirty patients with F-Dopa PET experienced FOG ('FOG group'). As basic characteristics did not match with the 98 non-FOG patients (nFOG), the FOG group was matched to an equally large nFOG sample ($N = 30$) concerning age, clinical follow-up duration and age at F-Dopa PET (see also Fig. 1). This was carried out by one investigator (A.H) without knowledge of F-Dopa results at the time of this assessment. Differences between groups were analyzed with the T-test or Mann–Whitney U-test, depending on normality. Two-tailed $p < 0.05$ was considered significant for all comparisons.

3. Results

3.1. General characteristics

UPDRS was assessed 3.0 ± 3.8 years (mean ± SD) after disease onset while F-Dopa PET was assessed 3.2 ± 3.9 years after disease onset. The dominant symptom side corresponded with reduced F-Dopa uptake in particularly the contralateral striatum (caudate 2.21 ± 0.29 and putamen 1.81 ± 0.24 versus ipsilateral caudate 2.29 ± 0.29 and putamen 1.94 ± 0.24). General characteristics including age, sex, and onset type symptom were similar for patients who either received or not received F-Dopa PET, as well as for patients with or without a recorded initial UPDRS.

3.2. F-Dopa PET related to tremor and hypokinesia-rigidity

For an initial assessment of F-Dopa characteristics and onset parkinsonian symptoms, we selected patients with PET measurements for which the onset symptom tremor ($N = 60$) or hypokinesia-rigidity ($N = 42$) was reported, thus allowing a global comparison between the two groups. F-Dopa uptake values in caudate and putamen of each hemisphere were used to assess a correlation with the lateralized onset symptoms in these groups. The hypokinesia-rigidity group, compared to the tremor group, showed reduced F-Dopa uptake in both putamen and caudate nucleus without, however, reaching statistical significance (putamen left 1.83 ± 0.25 and 1.96 ± 0.29, putamen right 1.85 ± 0.31 and 1.90 ± 0.26, caudate left 2.22 ± 0.29 and 2.32 ± 0.29, caudate right 2.17 ± 0.31 and 2.28 ± 0.28 for hypokinesia-rigidity and tremor, respectively). The main analysis of this study was subsequently performed using the first obtained UPDRS score, thus enabling the assessment of a relation between F-Dopa values and the severity of hypokinesia-rigidity and tremor in 79 PD patients. Left-sided UPDRS scores for hypokinesia-rigidity showed a negative correlation with F-Dopa PET dopamine uptake in the entire contralateral striatum (putamen $r = -0.343$; $p = 0.002$; caudate $r = -0.221$; $p = 0.049$). The right-sided UPDRS significantly correlated with reduced F-Dopa uptake in the left putamen ($r = -0.286$; $p = 0.010$) while such correlation remained sub-threshold for the left caudate nucleus ($r = -0.186$; $p = 0.093$). No relation was seen between UPDRS hypokinesia-rigidity scores and ipsilateral F-Dopa uptake. For the UPDRS tremor score, no significant correlations were seen with reduced F-Dopa uptake, neither in the contralateral nor in the ipsilateral striatum. The relation between the UPDRS sub-scores for each of the two cardinal PD symptoms and F-Dopa uptake is shown in Fig. 2.

3.3. F-Dopa PET related to freezing of gait

FOG patients had a follow-up duration of 8.1 ± 4.1 years, matching the selected nFOG patients (7.4 ± 4.0 years). The first record of FOG was 6.7 ± 3.9 years after the first visit, thus 2.7 ± 3.7 years after the F-Dopa PET. The (first recorded) UPDRS hypokinesia-rigidity items of both the left and right side were similar in the FOG and nFOG-groups, no significant difference was seen. Comparing the obtained PET measurement in the FOG-group with the matched nFOG revealed significantly lower F-Dopa uptake (mean ± SD) in the putamen of the right hemisphere (1.72 ± 0.29 versus nFOG 1.93 ± 0.29; $p = 0.005$). A similar group difference was seen for the left putamen without, however, reaching formal statistical significance ($p = 0.052$). Neither the right nor the left caudate nucleus showed a significant between-group difference. Within each group, F-Dopa uptake did not significantly differ between the opposite striatum nuclei (FOG caudate $p = 0.444$, putamen $p = 0.062$; nFOG caudate $p = 0.206$ and putamen $p = 0.627$).

4. Discussion

Investigating the association between striatum F-Dopa and the PD symptoms tremor and hypokinesia-rigidity, the registered onset symptom hypokinesia-rigidity and first taken UPDRS scores of this symptom revealed a clear correlation with reduced dopamine uptake in the contralateral striatum. In the equally large UPDRS group with quantitative data on tremor, no such correlation was seen. This underscores the difference in pathomechanisms underlying these symptoms, suggesting

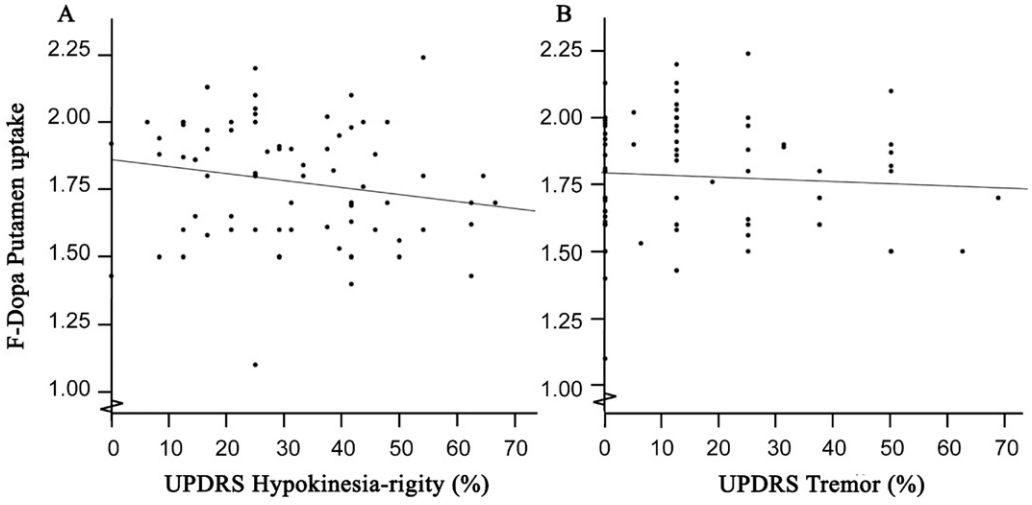

Fig. 2. Dominant symptom side related to contralateral F-Dopa putamen uptake. The UPDRS hypokinesia-rigidity values, $r = -0.187$, $p = 0.097^{*}$ (A) and the UPDRS tremor values, $r = -0.002$, $p = 0.987^{**}$ (B) are correlated with the contralateral dopamine uptake for the most affected side. UPDRS value is the patient UPDRS sub-score relative to the maximum sub-score. F-Dopa putamen uptake is expressed as the ratio relative to the occipital reference tissue. *Pearson correlation, **Spearman's correlation.

that striatum dopamine depletion inflicts hypokinesia-rigidity symptoms while another causal factor appears to generate PD tremor. Our retrospective PD study did not include healthy control subjects. Nevertheless, the finding that F-Dopa putamen uptake was lower than the caudate uptake, in both the hypokinesia-rigidity and tremor group, underscores the classical uptake profile seen in PD (Leenders et al., 1990; Eshuis et al., 2009); healthy subjects are characterized by an equal putamen-caudate distribution of F-Dopa uptake. While we are reluctant to infer specific differences in pathomechanisms underlying these two cardinal PD symptoms, our study provides solid arguments to maintain searching for such differences.

The observed correlation between hypokinesia-rigidity and F-Dopa uptake values is consistent with existing literature. The dissociation between hypokinesia-rigidity and tremor, without a specific dopamine deficit related to the latter, is firmly based on the large patient number in our study. Previous studies on the tremor-dopamine relation were contradicting, in which low patient numbers may have sometimes played a role (Benamer et al., 2003; Eggers et al., 2011; Isaias et al., 2007; Spiegel et al., 2007). Other reasons may have been the use of either 5-Dopa PET or FP-CIT SPECT, varying strategies of data analysis or disease stage. E.g., visual inspection of FP-CIT images has revealed less caudal striatum uptake in PD patients with hypokinesia-rigidity than in tremor (Eggers et al., 2011) while a direct comparison between F-Dopa uptake in such PD groups showed rostral uptake reduction in hypokinesia-rigidity (Eggers et al., 2014). Analysis of FP-CIT imaging data, including assessment of pallidum uptake additional to striatum measurements, and introducing a ratio between most and least affected side pointed at a correlation between tremor severity and reduced contralateral pallidum uptake (Helmich et al., 2011). In this respect, our large study with robust classical methods complements previous studies, allowing a convincing conclusion concerning the absence of a relation between the severity of tremor and striatum dopamine uptake. We had no data on pallidum F-Dopa uptake available, so we could not further explore the proposed link between pallidum dopaminergic deficit and cerebello-thalamic circuitry as a causal factor in PD tremor (Helmich et al., 2011).

Future studies combining (i) imaging modalities aimed at functional networks such as FDG-PET or resting-state fMRI with (ii) specific monaminergic PET tracers (Loane and Politis, 2011) appear to be most promising in getting the full picture on the differences in pathomechanisms underlying PD tremor and hypokinesia-rigidity. In such studies, attention needs to be given to disease duration because progression of PD over time particularly inflicts more hypokinesia-rigidity while tremor may stay rather stable (Eggers et al., 2012). In this respect, it may be noticed that the mean interval of 3.2 years between first recalled symptom and F-Dopa PET was relatively short in our study. This issue is particularly urgent because the ongoing decrease of F-Dopa uptake during disease progression is not evenly distributed within the basal ganglia. The early stage assessment in our study is due to the retrospective nature of our study; patients were scanned for diagnostic reasons while their follow-up provided the opportunity to exclude possible patients who turned out not to suffer from PD. On the other hand, retrospective data analysis implied that were not able to get a UPDRS score of all 129 patients that underwent F-Dopa PET. Although this might limit the interpretation of the results, the remaining group of 79 patients is still large enough to draw conclusions from. Furthermore, the basis characteristics did not differ between patients that did and did not receive a F-Dopa PET scan.

FOG showed bilaterally reduced putamen uptake, which only reached statistical significance in the right hemisphere. F-Dopa depletion in FOG compared to nFOG patients has been reported before (Giladi et al., 2001). Although a levodopa-independent state may play a role in FOG, approaching FOG as a dopamine-responsive symptom is generally advised (Nonnekes et al., 2015). In our results, the deficit appears to be localized in the putamen more than the caudate nucleus. Using voxel-based statistical parametric analysis, which included normalization steps in global uptake, a relation between FOG and particularly right hemisphere impairment has previously been suggested (Giladi et al., 2000; Bartels et al., 2006; van der Hoorn et al., 2014). The present research only hints at such asymmetry without statistically support. It should be considered, in this respect, that FOG emerged as a relative late symptom during follow-up of the patients in our study, while the (first recorded) UPDRS and F-Dopa uptake were assessed at relative early disease stages, indeed preceding the symptom. One might speculate that asymmetry in F-Dopa uptake was an early marker of this symptom which could have reached statistical significance at the stage of overt FOG.

5. Conclusion

Our large patient group demonstrated that increased severity of hypokinesia-rigidity symptoms correlated with reduced dopamine uptake values measured with F-Dopa PET. For UPDRS tremor symptoms no such correlation was found. Furthermore, freezing of gait correlated with lower F-Dopa uptake in the putamen.

Financial disclosure

None.

Acknowledgments

None.

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