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

Angelina R.A. Pikstra[a], Anouk van der Hoorn[a,b,*], Klaus L. Leenders[a], Bauke M. de Jong[a]

[a]Department of Neurology, University Medical Centre Groningen, University of Groningen, The Netherlands
[b]Department of Radiology, University Medical Centre Groningen, University of Groningen, The Netherlands

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

* Corresponding author at: Department of Radiology (EB44), University Medical Center Groningen, Hanzeplein 1, P.O. Box 30.001, 9700 RB Groningen, The Netherlands.
E-mail addresses: a.r.a.pikstra@umcg.nl (A.R.A. Pikstra), a.van.der.hoorn@umcg.nl (A. van der Hoorn), k.l.leenders@umcg.nl (K.L. Leenders), b.m.de.jong@umcg.nl (B.M. de Jong).

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-

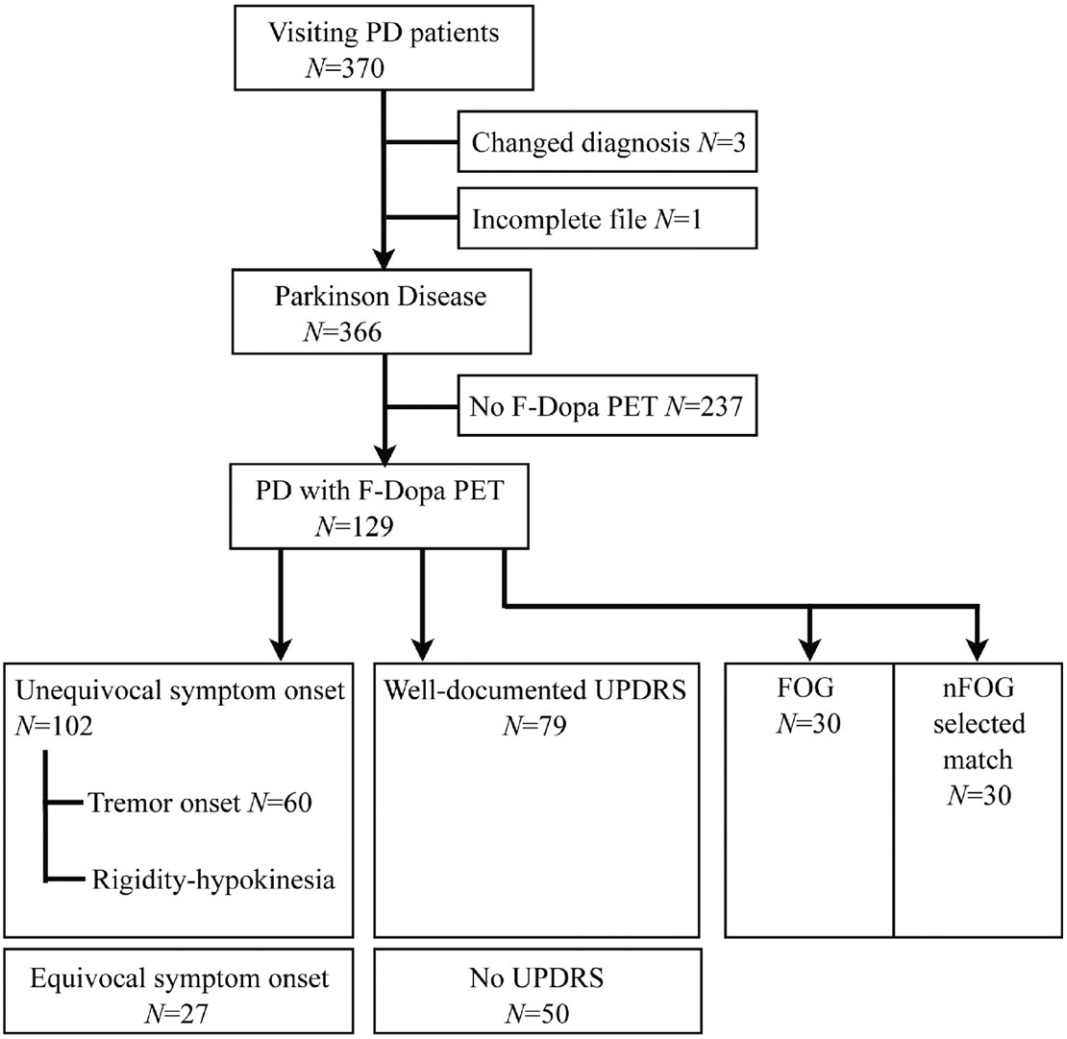

Fig. 1. The flow diagram showed the distributions of PD patients.