Parkinsonism and Related Disorders xxx (2018) 1–6

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Presynaptic striatal dopaminergic depletion predicts the later development of freezing of gait in *de novo* Parkinson's disease: An analysis of the PPMI cohort

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ARTICLE INFO

Article history:
Received 22 December 2017
Received in revised form
23 February 2018
Accepted 27 February 2018

Keywords:
Parkinson's disease
Freezing of gait
Caudate
Putamen
DAT

ABSTRACT

Introduction: The current study was designed to determine whether the degree of presynaptic striatal dopamine depletion can predict the later development of freezing of gait (FOG) in Parkinson's disease (PD).

Methods: This retrospective cohort study included 390 *de novo* patients with PD without FOG at baseline. The participants were divided into tertiles according to the baseline dopamine transporter (DAT) uptake of each striatal subregion, and the cumulative risk of FOG was compared using the Kaplan-Meier method. Cox proportional hazard models were used to assess the predictive power of DAT uptake of striatal subregions for the development of FOG.

Results: During a median follow-up period of 4.0 years, 143 patients with PD (36.7%) developed FOG. The severe reduction group of DAT uptake in the caudate nucleus and putamen had a significantly higher incidence of FOG than that of the mild and moderate reduction groups. Multivariate Cox regression analyses showed that DAT uptakes in the caudate nucleus (hazard ratio [HR] 0.551; 95% confidence interval [CI] 0.392–0.773; $p = 0.001$) and putamen (HR 0.441; 95% CI 0.214–0.911; $p = 0.027$) predicted the development of FOG. In addition, male sex, higher postural instability and gait difficulty score, and a lower Montreal Cognitive Assessment score were also significant predictors of FOG.

Conclusion: Our finding suggests that presynaptic striatal dopaminergic denervation predicts the later development of FOG in *de novo* patients with PD, which may provide reliable insight into the mechanism of FOG in terms of nigrostriatal involvement.

1. Introduction

Freezing of gait (FOG) is characterized by an inability to generate effective stepping with an unpredictable and transient nature [1]. In advanced Parkinson's disease (PD), FOG is one of the most disabling motor symptoms which is associated with an increased risk for falls and injuries, loss of independence, and impaired quality of life [2,3]. One randomized clinical trial has shown that FOG developed in approximately a quarter of the patients with early PD over 2 years [4], and cohort studies have reported that more than 60% of patients with PD experienced it over a period of 10 or 12 years [5,6].

A variety of factors related to FOG have been identified in patients with PD, including male sex [7], longer disease duration [2,4,7,8], increased motor severity [2,4,7], severe postural instability and gait difficulty [2,4,5], and lower cognitive performance [9,10]. Although the mechanism for FOG is not completely understood, presynaptic striatal dopamine depletion is considered to have an important role in its manifestation. This hypothesis is supported by functional imaging studies where PD patients with FOG had a lower dopamine transporter (DAT) activity in the

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https://doi.org/10.1016/j.parkreldis.2018.02.047
1353-8020/

caudate nucleus, putamen, or both compared to those without FOG [11–13]. However, these observations were obtained from a small number of patients and were limited to the cross-sectional correlation.

Therefore, the aim of the current study is to determine whether the degree of presynaptic dopamine depletion in the caudate nucleus, putamen, or both in the early *de novo* stage can predict the later development of FOG in patients with PD using longitudinal data. We investigated their relationship by quantitatively analyzing the ^{123}I-Ioflupane DAT single photon emission computed tomography (SPECT) data from the Parkinson's Progression Markers Initiative (PPMI) cohort study.

2. Methods

2.1. Study design and participants

PPMI is an international multicenter, observational cohort study designed to discover and validate biomarkers that predict the heterogeneous progression of PD. The methodology and details of the study assessments have been published elsewhere [14] and are available on the PPMI website (http://ppmi-info.org/study-design).

At enrollment, PD participants were required to 1) be aged 30 years or older at diagnosis; 2) have an asymmetric resting tremor or asymmetric bradykinesia, or two of following: bradykinesia, resting tremor, and rigidity; 3) have been recently diagnosed within 2 years of study enrollment; 4) have a Hoehn and Yahr stage of 1 or 2; 5) be untreated for PD; and 6) have a DAT deficit on the ^{123}I-Ioflupane-SPECT imaging. In this study, we included PD participants only with a score of 0 in both the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) item 2.13 (freezing) and item 3.11 (freezing of gait) at baseline visit. The data were downloaded from the PPMI database on June 19, 2017.

2.2. Standard protocol approvals, registrations, and consents

Each participating PPMI site received approval from an ethical standards committee on human experimentation before the start of the study and obtained written informed consent for research from all participating individuals in the study.

2.3. Assessment of FOG

Patients with PD from the PPMI study are followed up at 3 month intervals in the first year, 6 month intervals in the subsequent four years, and 12 month intervals in the last three years. If a subject withdraws early from the study or will begin symptomatic therapy, additional follow-up may need to be done prior to the regular visit schedule. In this study, FOG was defined to be present if the score was 1 or greater on either the MDS-UPDRS item 2.13 or item 3.11 at any point during the follow-up period. The MDS-UPDRS item 2.13 categorizes symptoms experienced over the preceding week into 5 levels: 0, no freezing; 1, freezing without subsequent start hesitation; 2, freezing with subsequent start hesitation; 3, need a walking aid or someone's help occasionally; and 4, need a walking aid or someone's help most or all of the time. In the evaluation of the MDS-UPDRS item 3.11, patients were asked to walk at least 10 m, then turn around and return to the examiner. This item also categorizes into 5 levels: 0 no freezing; 1, freezing on starting, turning or walking through doorway with a single halt; 2, freezing on starting, turning or walking through doorway with more than single halt; 3, freezing once during straight walking; and 4, freezing multiple times during straight walking.

2.4. DAT SPECT imaging

SPECT studies were done during the screening visit before enrollment. All participants received 111–185 MBq (3–5mCi) of ^{123}I-Ioflupane intravenously, and the acquisition was performed between 3.5 and 4.5 h following the injection. Raw projection data were acquired with a 128×128 matrix in a step and shoot mode and then were imported to the Hermes software (Medical Solutions, Stockholm, Sweden) for iterative reconstruction. The reconstructed files were transferred to Pmod (PMOD Technologies, Zurich, Switzerland) for subsequent processing. Regions of interest were placed on the left and right caudate, the left and right putamen, and the occipital cortex as a reference tissue. The striatal binding ratio for each of the 4 striatal regions was calculated as follows: [(target region/reference region) − 1] [15]. For this analysis, we used the mean DAT uptake of the left and right side in each caudate nucleus and putamen, respectively.

2.5. Variables

Motor symptoms were assessed using the MDS-UPDRS part 3. Tremor score and postural instability and gait difficulty (PIGD) score were calculated using the MDS-UPDRS part 2 and part 3 [16]. The tremor score was the sum of the following eleven items: 2.10 (tremor), 3.15a (postural tremor RUE), 3.15b (postural tremor LUE), 3.16a (kinetic tremor RUE), 3.16b (kinetic tremor LUE), 3.17a (rest tremor RUE), 3.17b (rest tremor LUE), 3.17c (rest tremor RLE), 3.17d (rest tremor LLE), 3.17e (rest tremor lip/jaw), and 3.18 (rest consistency). The PIGD score was the sum of the following three items: 2.12 (walking and balance), 3.10 (gait), and 3.12 (postural stability). Overall cognitive status was assessed with the Montreal Cognitive Assessment (MoCA).

2.6. Statistical analysis

The comparison of the DAT uptake according to the presence or absence of FOG at baseline was done with the Mann-Whitney *U* test. The participants were divided into tertiles according to the baseline DAT uptake level of each striatal subregion. To compare the baseline demographic and clinical variables among the subgroups, we used the Pearson χ^2 test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. If appropriate, Bonferroni post-hoc test was employed next. We used the Kaplan-Meier method to estimate the cumulative risk of FOG in each subgroup and assessed differences with the log-rank statistic. Cox proportional hazard models were used to perform an adjusted analysis of the association between the initial DAT uptake and the subsequent FOG. In addition to the DAT uptake of each striatal subregion, other potential predictor variables such as sex, disease duration, age at onset, MDS-UPDRS motor score, tremor score, PIGD score, and MoCA score were included in the Cox proportional hazard models, which were selected based on previously reported associations and clinical knowledge. All variables with a p value less than 0.2 in the univariate models were included in a backward elimination procedure with a p value removal of 0.1. To avoid a collinearity issue between the caudate and putamen DAT uptakes, two multivariate cox regression models were used. The level of statistical significance was set at a p value < 0.05. Calculations were performed with SPSS 18.0 (SPSS, Chicago, IL).

3. Results

A total of 423 patients with PD were enrolled into the PPMI study between July 1, 2010, and May 31, 2013. Of these, 4 patients had no ^{123}I-Ioflupane-SPECT imaging data and were excluded. At

Please cite this article in press as: R. Kim, et al., Presynaptic striatal dopaminergic depletion predicts the later development of freezing of gait in *de novo* Parkinson's disease: An analysis of the PPMI cohort, Parkinsonism and Related Disorders (2018), https://doi.org/10.1016/j.parkreldis.2018.02.047