Parkinsonism and Related Disorders xxx (2018) 1–6

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Weight loss is associated with rapid striatal dopaminergic degeneration in Parkinson's disease

Kyoungjune Pak [a], Hae Kyung Shin [b], Eun-Joo Kim [b], Jae-Hyeok Lee [c, d], Chul Hyoung Lyoo [e], Jongsang Son [f, g], Myung Jun Lee [b, *]

[a] Department of Nuclear Medicine, Pusan National University Hospital, Pusan National University School of Medicine and Biomedical Research Institute, Busan, Republic of Korea
[b] Department of Neurology, Pusan National University Hospital, Pusan National University School of Medicine and Biomedical Research Institute, Busan, Republic of Korea
[c] Department of Neurology, Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Beomo-ri, Mulgum-eup, Yangsan, Gyeongsangnam-do, Republic of Korea
[d] Medical Research Institute, Pusan National University School of Medicine, Yangsan, Republic of Korea
[e] Department of Neurology, Gangnam Severance Hospital, Yonsei University Medical College, Seoul, Republic of Korea
[f] Sensory Motor Performance Program, Rehabilitation Institute of Chicago, Chicago, IL, USA
[g] Department of Physical Medicine & Rehabilitation, Northwestern University, Chicago, IL, USA

ARTICLE INFO

Article history:
Received 6 January 2018
Received in revised form
21 February 2018
Accepted 27 February 2018

Keywords:
Parkinson disease
Weight loss
Body mass index
^{123}I-FP-CIT
SPECT

ABSTRACT

Introduction: Weight loss in Parkinson's disease (PD) is associated with poorer clinical outcomes and rapid disease progression. However, it is unclear whether a longitudinal association between weight loss and striatal dopaminergic degeneration exists.

Methods: Using data from 171 PD patients in the Parkinson's Progression Markers Initiative (PPMI) cohort, we investigated longitudinal associations of change in body mass index (BMI) with striatal dopaminergic activity on ^{123}I-*N*-3-fluoropropyl-2-beta-carboxymethoxy-3beta-(4-iodophenyl) nortropane (^{123}I-FP-CIT) single positron emission computed tomography (SPECT). We defined BMI loss as a reduction in BMI value > 5% of baseline, and categorized the PD patients into 2 subgroups (patients with and without BMI loss). Linear mixed model (LMM) analysis was employed to compare the progression of striatal dopaminergic degeneration.

Results: In LMM analyses, BMI values in PD patients were not correlated with clinical severities of parkinsonian motor deficits, cognitive impairment and depressive mood. However, BMI values were positively associated with changes in striatal ^{123}I-FP-CIT binding over 24 months (caudate nucleus, estimate $= 9.37 \times 10^{-3}$, $p = 0.009$; putamen, estimate $= 7.04 \times 10^{-3}$, $p = 0.031$). Patients with BMI loss exhibited greater deterioration of striatal dopaminergic activity than those without (caudate nucleus, estimate $= 3.35 \times 10^{-3}$, $p = 0.008$; putamen, estimate $= 2.34 \times 10^{-3}$, $p = 0.025$).

Conclusion: Our findings suggest a potential association between striatal dopaminergic activity with body weight or impairment in energy homeostasis. Body weight and its change may be a clinical biomarker reflecting striatal dopaminergic dysfunction in PD.

1. Introduction

Approximately half of Parkinson's disease (PD) patients experience unintentional weight loss during the course of their disease [1,2]. Weight loss is associated with poorer clinical outcomes including a greater severity of parkinsonian motor deficits, more frequent dementia and increased morbidity and mortality [3,4]. It has been proposed that an imbalance between energy intake and expenditure may cause weight loss in PD [5–7]. However, the precise mechanism is still unclear.

Previous longitudinal studies in PD patients have demonstrated that patients with weight loss show a rapid progression in motor deficits and disease stage [3,8,9], suggesting a possible association

* Corresponding author. Department of Neurology, Pusan National University Hospital, Pusan National University School of Medicine and Biomedical Research Institute, Gudeok-ro 179, Seo-gu, Busan, 49241, Republic of Korea.
E-mail addresses: mslayer9@gmail.com, mslayer9@pusan.ac.kr (M.J. Lee).

https://doi.org/10.1016/j.parkreldis.2018.02.044
1353-8020/

between weight loss and neurodegenerative process in PD. Indeed, a neuroimaging study using dopamine transporter (DAT) scans reported a significant correlation between striatal dopaminergic activity and body mass index (BMI) at diagnosis [10]. Nigrostriatal dopaminergic dysfunction in PD is associated with severities of clinical features such as parkinsonian motor deficits, hyposmia and depressive mood [11–13], which can interfere in the balance between energy intake and expenditure [14].

However, a longitudinal association between body weight and striatal dopaminergic dysfunction has not previously been undertaken in PD patients. Thus, it remains unclear whether changes in body weight may be associated with progression of dopaminergic degeneration. Using the database of the Parkinson's Progression Markers Initiative (PPMI) cohort, we investigated the association between BMI loss with progression of striatal dopaminergic dysfunction using ^{123}I-*N*-3-fluoropropyl-2-beta-carboxymethoxy-3beta-(4-iodophenyl) nortropane (^{123}I-FP-CIT) single positron emission computed tomography (SPECT).

2. Patients and methods

2.1. Subjects

Anonymized and de-identified data from the PPMI database (http://www.ppmi-info.org/data) was downloaded in March 2017. PPMI is an ongoing observational cohort study aimed at identifying biomarkers of PD progression. At baseline, PD patients were required to be older than 30 years of age, diagnosed with PD within the past 2 years, have a Hoehn and Yahr (H&Y) stage not larger than II, be untreated, and exhibited striatal dopamine deficits on ^{123}I-FP-CIT SPECT. Subjects were excluded from the PPMI database if they had a clinical diagnosis of dementia, received drugs that might interfere with ^{123}I-FP-CIT SPECT within the past 6 months, were being administered with anticoagulants, had any other medical or psychiatric condition or laboratory abnormality, had taken investigational drugs or devices within 60 days prior to baseline, or who showed evidence of clinically significant neurological disorders in magnetic resonance imaging. The data were collected from over 33 clinical sites in 11 countries. The PPMI study was approved by the local Institutional Review Boards (IRBs) of all participating sites and written informed consent was obtained from each subject at the time of enrollment for imaging data and clinical measurements. The detailed information and complete list of IRBs for the PPMI sites can be found at http://www.ppmi-info.org.

We included data for PD patients in the PPMI cohort with: i) annual measurement of weight and height for 4 years, and ii) ^{123}I-FP-CIT SPECT imaging taken 2 or more times. PD patients were excluded if they had: i) diagnosis of malignancy or dementia during the study period, ii) deep brain stimulation or other surgical intervention for PD, iii) other chronic illness possibly causing weight loss such as congestive heart failure, asthma, chronic obstructive pulmonary disease, untreated thyroid disorder, HIV infection and untreated pulmonary tuberculosis.

2.2. BMI-change subsets and clinical measurements

We used records of height and weight at baseline, and 12-, 24-, 36- and 48-months follow-up. BMI was calculated using the standard formula: weight (kg)/height^2 (m^2). To investigate the association of BMI change with the progression of striatal DAT binding and clinical measurements, PD patients were categorized into 2 subgroups, i.e. subsets with or without BMI loss. BMI loss was defined as reduction of BMI values > 5% of baseline: [(BMI at 12-, 24-, 36- or 48-months follow-up − BMI at baseline)/BMI at baseline] [5].

To test the association between clinical features and BMI, we used the results of clinical examination including Movement Disorder Society sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part II, III and IV, the geriatric depression scale (GDS), Montreal Cognitive Assessment (MoCA), Schwab and England Activity of Daily Living (ADL) score, and Scale for Outcomes in Parkinson's disease - Autonomic (SCOPA-AUT). Levodopa-induced dyskinesia (LID) subscores (summation of MDS-UPDRS IV items 1 and 2) were calculated to investigate a potential impact of LID on weight loss of PD patients.

2.3. ^{123}I-FP-CIT SPECT scan and image processing

In the PPMI cohort, ^{123}I-FP-CIT SPECT scans were performed at baseline, and 12-, 24- and 48-month follow-up. SPECT images were acquired 4 ± 0.5 h after injection of 111–185 MBq of ^{123}I-FP-CIT. Subjects were pretreated with iodine solution or perchlorate prior to injection to block thyroid uptake. Raw data were acquired into 128 × 128 matrix stepping each at 3 or 4° for the total projections. Raw projection data were reconstructed using iterative ordered subset expectation maximization with HERMES (Hermes Medical Solutions, Stockholm, Sweden). The reconstructed images were transferred to pmod (PMOD Technologies LLC, Zürich, Switzerland) for subsequent processing including attenuation correction.

Downloaded scans were loaded using pmod v3.6 (PMOD Technologies LLC, Zürich, Switzerland) with ^{123}I-FP-CIT template [15]. Specific binding of ^{123}I-FP-CIT in DAT was calculated using a region of interest analysis. A standard set for volume of interest (VOI) defining the caudate nucleus and putamen was based on the Automated Anatomical Labeling (AAL) atlas [16]. The cerebellum was chosen as a reference region. The VOI template was applied to measure specific binding ratio (SBRs) of the caudate nucleus and putamen as follows: SBR = (target − cerebellum)/cerebellum. The mean SBRs of both hemisphere were calculated for each individual.

From the baseline to 48-months follow-up, 137 of 171 PD patients received ^{123}I-FP-CIT SPECT imaging 3 times. 18 patients had DAT scans 4 times, and remaining 16 subjects received it twice over 4 years of follow-up. 171 PD patients underwent ^{123}I-FP-CIT SPECT scans at baseline and 12-months follow-up. 155 patients underwent the same imaging at 24-months follow-up. However, only a small portion of subjects (n = 18) at 48-months follow-up underwent a DAT scan. To avoid a possible bias from the small subject number, results of DAT scan at 48-months follow-up were not included in the statistical analyses.

2.4. Statistical analyses

For continuous variables satisfying Gaussian distribution, we compared variables between BMI change subsets using independent *t*-test and analysis of covariance (ANCOVA) covariated with age, gender and disease duration. Mann-Whitney *U* test was used for comparisons in continuous variables not satisfying Gaussian distribution. Chi-square test was used for comparison of categorical variables.

To demonstrate the association of BMI (continuous variable) and BMI change subsets (categorical variable) with striatal ^{123}I-FP-CIT SBRs, we employed a linear mixed model (LMM). Striatal DAT binding was defined as the dependent variable in the LMMs. Fixed effects included age, gender, time interval from baseline (months), and BMI or BMI change subsets. Interaction between BMI change subsets and time interval from baseline was added to the fixed effect in order to compare slopes of the decrement in striatal DAT SBRs between BMI change subsets. In addition, longitudinal associations between BMI and clinical measurements for 4 years were tested by LMMs using clinical measurement as a dependent variable. Multiple statistical tests were undertaken with several null hypotheses tested,

Please cite this article in press as: K. Pak, et al., Weight loss is associated with rapid striatal dopaminergic degeneration in Parkinson's disease, Parkinsonism and Related Disorders (2018), https://doi.org/10.1016/j.parkreldis.2018.02.044