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Premorbid exercise engagement and motor reserve in Parkinson's disease

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ABSTRACT

Background: Life-long experiences of cognitive activity could enhance cognitive reserve, which may lead individuals to show less cognitive deficits in Alzheimer's disease, despite similar pathological changes. We performed this study to test whether premorbid physical activity may enhance motor reserve in Parkinson's disease (PD) (i.e., less motor deficits despite similar degrees of dopamine depletion).
Methods: We assessed engagement in premorbid leisure-time exercise among 102 drug naive PD patients who had been initially diagnosed at our hospital by dopamine transporter scanning. Patients were classified into tertile groups based on the frequency, duration, and intensity of the exercises in which they participated.
Results: Among patients with mild to moderate reductions in striatal dopaminergic activity (above the median dopaminergic activity), the exercise group of the highest tertile showed significantly lower motor scores (i.e., fewer motor deficits, 15.53 ± 6.25), despite similar degrees of dopamine reduction, compared to the combined group of the middle and the lowest tertiles (21.57 ± 8.34, $p = 0.01$). Nonetheless, the highest tertile group showed a more rapid decline in motor function related to reductions in striatal dopaminergic activity than the other two groups ($p = 0.002$ with the middle tertile group and $p = 0.001$ with the lowest tertile group).
Conclusions: These results suggest that engagement in premorbid exercise acts as a proxy for an active reserve in the motor domain (i.e., motor reserve) in patients with PD.

1. Introduction

The concept of cognitive reserve (CR) explains the differences between individuals in their susceptibility to age-related brain changes or pathologies related to Alzheimer's disease (AD) [1]. Epidemiological studies suggest that lifelong experiences, including educational and occupational attainment, and participation in leisure activities in later life can enhance CR [1]. An enhanced CR may slow cognitive aging, reduce the risk of dementia, and lead to less cognitive deficits despite severe pathological lesions [1]. A previous study showed that the risk of developing dementia in individuals with a lower educational level or lower lifetime occupational attainment was 2–2.5 times higher than that in those with a higher educational level or higher occupational attainment [2]. As well, neuroimaging and post-mortem studies have indicated that AD pathology is more advanced in patients with a higher CR than in those with a lower CR, even though they appear clinically similar [3,4].

Parkinson's disease (PD) is mainly characterized by motor dysfunction related to striatal dopaminergic depletion. Similar to the concept of CR in relation to neurodegenerative disorders, we hypothesized that the presence of motor reserve (MR) explains the individual differences in motor deficits despite similar pathological changes in PD. Animal experiments have shown that enhanced

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physical training may protect dopamine neurons from various parkinsonism-inducing neurotoxins [5,6]. Additionally, epidemiological studies have demonstrated that long-term strenuous exercises are associated with a lower PD risk in humans [7,8]. Accordingly, just as premorbid cognitive activity enhances an individual's CR, premorbid physical activity (i.e., engagement in exercise) may enhance MR in PD. To address this hypothesis, we investigated whether the engagement in premorbid exercise affects the relationship between striatal dopaminergic depletion and the severity of motor deficits in early, drug-naïve, patients with PD.

2. Methods

2.1. Participants

We conducted a prospective survey on engagement in premorbid exercise among patients with PD who had been newly diagnosed at Yonsei Parkinson Center from February 2008 to October 2012. All patients underwent dopamine transporter imaging using [^{18}F] *N*-(3-Fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane positron emission tomography (FP-CIT PET) scans for the work-up for their parkinsonian symptoms. PD was diagnosed according to both the clinical criteria of the UK Brain Bank [9], the presence of appropriate dopamine transporter defects on FP-CIT-PET scans [10], and the presence of PD drug response during follow-up (≥6 months). Patients who had any focal neurological deficit other than Parkinsonism or had cognitive dysfunction (mini-mental status examination [MMSE] score lower than 24) were excluded. Part III of the Unified Parkinson Disease rating scale (UPDRS-motor) was used to assess PD severity, and Beck Depression Inventory (BDI) was used to evaluate the presence of depression in each patient. Both FP-CIT-PET scans and UPDRS-motor measurements were performed in drug-naïve state in all patients. Informed consent was obtained from all patients and the Ethics committee of our hospital reviewed and approved this study.

2.2. Assessment of engagement in premorbid exercise

Premorbid exercise engagement was assessed via patient interviews using a survey based on the Physical Activity Scale for the Elderly (PASE) and its Korean version (K-PASE) [11,12]. The PASE (and K-PASE) is a brief, easily-scored, reliable, and valid instrument for the assessment of physical activity in epidemiological studies of older people, and consists of questions related to leisure exercise, household work, and job-related standing/walking [11,12]. Among the questions included in the PASE, we asked participants to report how often and for how long they had engaged in five items related to leisure exercises; 1) walking outside the home, 2) light sports activity (bowling, fishing, and similar activities), 3) moderate sports activity (skating, soccer, ballroom dancing, and similar activities), 4) strenuous sports activity (tennis, jogging, cycling, and similar activities), and 5) muscle strength/endurance training (weight-lifting, push-up exercise and similar activities). Total premorbid exercise score (PES) was calculated for each patient as (the mean number hours per day engaging in each activity during a week) × (the PASE-weight score of each activity) × (years engaged in each activity prior to the onset of PD) (Table 1). The PASE-weight score were 20 for walking outside the home, 21 for light sports, 23 for both moderate and strenuous sports, and 30 for muscle-strengthening exercise [11,12]. We classified the patients into the three groups according to their PES (the highest, the middle, and the lowest tertile groups).

2.3. PET-CT image acquisition

For assessing striatal dopamine depletion, we obtained dopamine transporter scans using ^{18}F-FP-CIT with a GE Discovery STe (DSTE) PET-CT scanner (GE Healthcare Technologies, Milwaukee, WI). All participants fasted for at least 6 h before scanning. Then each patient received an intravenous injection of 5 mCi (185 MBq) of ^{18}F-FP-CIT. We obtained dopamine transporter images in a 3D mode during a 20-minute session that took place 90 min after each injection, and performed a post hoc 3D Gaussian smoothing with a 2.3 mm full width half maximum. For localization and attenuation correction, CT images were acquired at 120 KVp and 380 mAs after PET scanning.

2.4. Quantitative analysis of ^{18}F-FP-CIT PET data

Quantitative analyses of ^{18}F-FP-CIT PET data were performed according to a previously published methodology [10]. Image processing was performed using SPM8 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, UCL, London, UK) with MATLAB 2013a for Windows (MathWorks, Natick, MA). Quantitative analyses were based on volumes of interests (VOIs), which were defined based on a template in standard space. To remove inter-subject anatomical variability, all reconstructed PET images were spatially normalized to the Montreal Neurology Institute template space using a standard ^{18}F-FP-CIT PET template, which was made using ^{18}F-FP-CIT PET and T1 MRI images of 13 normal controls. Twelve VOIs of bilateral striatal subregions and one occipital VOI were drawn on a co-registered spatially normalized single T1 MRI and ^{18}F-FP-CIT PET template image on MRIcro version 1.37 (Chris Rorden, Columbia, SC), as in a previous study [10]. These VOIs were adjusted by a minor translation in our in-house VOI editing software called ANTIQUE [13]. Using dopamine transporter activity concentrations in each VOI, we estimated the surrogate of nondisplaceable binding potential (BPnd), which was defined as (the mean standardized uptake value [SUV] of the striatal subregions VOI - the mean SUV of the occipital VOI)/(the mean SUV of the occipital VOI) [14].

2.5. Statistical analyses

Data were expressed as means ± SDs. One-way ANOVA was used to compare numeric variables, and χ^2 analysis was used to compare non-parametric variables among different exercise groups. Unpaired *t*-test was used to compare numeric variables between the two groups. Pearson's correlation analysis was conducted to evaluate the relationship between UPDRS-motor scores and BPnd in the posterior putamen. Also, we analyzed differences in the correlated coefficients among the exercise groups using Steiger's Z-test. A general linear model was used to compare the difference in UPDRS-motor scores among the exercise groups after controlling for age, gender, symptom duration, education duration, mini-mental status examination score, and BPnd in the posterior putamen. We also tested the interaction effect between BPnd in the posterior putamen and the exercise groups to assess whether the association of UPDRS-motor score and BPnd in the posterior putamen differed among the groups. SPSS Statistics version 20 (IBM SPSS, Armonk, NY, USA) was used to perform all statistical analyses. *P*-values <0.05 were regarded as significant.

3. Results

One hundred and two patients (mean age, 62.9 ± 9.4 years; range, 37–83 years; 50 men) were included in the data analysis. Mean symptom duration was 1.3 ± 1.3 years, mean UPDRS-motor

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