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Non-exercise physical activity attenuates motor symptoms in Parkinson disease independent from nigrostriatal degeneration

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ABSTRACT

Objective: To investigate the relationship between time spent in non-exercise and exercise physical activity and severity of motor functions in Parkinson disease (PD).

Background: Increasing motor impairments of PD incline many patients to a sedentary lifestyle. We investigated the relationship between duration of both non-exercise and exercise physical activity over a 4-week period using the Community Health Activities Model Program for Seniors (CHAMPS) questionnaire and severity of clinical motor symptoms in PD. We accounted for the magnitude of nigrostriatal degeneration.

Methods: Cross-sectional study. PD subjects, n = 48 (40 M); 69.4 ± 7.4 (56–84) years old; 8.4 ± 4.2 (2.5–20) years motor disease duration, mean UPDRS motor score 27.5 ± 10.3 (7–53) and mean MMSE score 28.4 ± 1.9 (22–30) underwent [^{11}C]dihydrotetrabenazine (DTBZ) PET imaging to assess nigrostriatal denervation and completed the CHAMPS questionnaire and clinical assessment.

Results: Bivariate correlations showed an inverse relationship between motor UPDRS severity scores and duration of non-exercise physical activity ($R = -0.37$, $P = 0.0099$) but not with duration of exercise physical activity ($R = -0.05$, $P = 0.76$) over 4 weeks. Multiple regression analysis using UPDRS motor score as outcome variable demonstrated a significant regressor effect for duration of non-exercise physical activity ($F = 6.15$, $P = 0.017$) while accounting for effects of nigrostriatal degeneration ($F = 4.93$, $P = 0.032$), levodopa-equivalent dose (LED; $F = 1.07$, $P = 0.31$), age ($F = 4.37$, $P = 0.043$) and duration of disease ($F = 1.46$, $P = 0.23$; total model ($F = 5.76$, $P = 0.0004$).

Conclusions: Non-exercise physical activity is a correlate of motor symptom severity in PD independent of the magnitude of nigrostriatal degeneration. Non-exercise physical activity may have positive effects on functional performance in PD.

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1. Introduction

There is growing evidence of an association between physical inactivity and negative outcomes in patients with PD, including impaired activities of daily living and gait instability [1,2]. Axial motor dysfunctions in Parkinson disease (PD) [3] – which are generally the least responsive to dopaminergic therapy – incline patients towards a sedentary lifestyle [4], with a resulting increased risk for the negative consequences of physical inactivity [5]. The Sydney Multicenter Study of PD, for example, found that dopamine non-responsive problems dominate 15 years after initial assessments and include frequent falls, which occurs in 81% of the patients [6]. Patients with more severe postural and gait difficulties (PIGD) problems may also develop 'fear-of-falling,' and become even more sedentary [3]. This may contribute to decreases in

Abbreviations: CHAMPS, Community Health Activities Model Program for Seniors questionnaire; DTBZ, dihydrotetrabenazine; LED, levodopa equivalent dose; PD, Parkinson disease; PET, positron emission tomography; UPDRS, Unified Parkinson's Disease Rating Scale; VMAT2, vesicular monoamine transporter type 2.

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muscle strength and 'deconditioned' postural reflexes, further exacerbating the motor decline caused by the disease process itself [7,8]. A vicious cycle of worsening parkinsonism and increasingly sedentary behavior may explain decreasing physical activity in advanced PD. This vicious cycle raises a 'chicken and egg' mechanistic question where it is generally assumed that declining physical activity levels reflect the effects of increasingly severe nigrostriatal losses as an increasingly limiting factor in motor capacity and physical activity. It is also plausible that lack of physical activity worsens motor symptom severity in PD independent of the degree of nigrostriatal degeneration. The latter hypothesis is in keeping with an emerging body of literature in exercise physiology that both levels of general activity and levels of vigorous exercise have independent effects on health outcomes [5,9]. A person meeting recommended weekly exercise guidelines may still be at risk of negative health effects if the remainder of the week consists of sedentary behavior [5].

Understanding to what degree physical activity (as determined by the hourly durations of vigorous exercise and non-exercise physical activity) is associated with motor symptom severity in PD independent of the degree of nigrostriatal degeneration requires objective assessment of the integrity of dopaminergic nerve terminals in the living brain of patient with PD. Positron emission tomography (PET) allows measurement of nigrostriatal dopaminergic nerve terminal density. PET imaging using vesicular monoamine transporter type 2 (VMAT2) ligands quantifies nigrostriatal nerve terminal reductions in PD subjects reflecting neurodegeneration of dopaminergic neurons used to assess disease severity objectively [10,11].

The aim of this cross-sectional study was to investigate the relationship between duration of time spent in vigorous exercise and non-exercise physical activity and severity of motor functions in PD while accounting for the degree of nigrostriatal degeneration using VMAT2 brain PET imaging. We performed a within-group analysis of PD subjects to test our hypothesis that the degree of physical activity (defined in our study as the combination of vigorous exercise and non-exercise physical activity) influences the expression of clinical motor symptom severity independent of the degree of nigrostriatal dopaminergic denervation. This study addresses a gap in our knowledge as it addresses the effects of physical activity and clinical expression of motor symptoms in PD while taking into account the quantitative relationship between parkinsonian motor symptoms and loss of dopaminergic nerve terminal using an objective in vivo biomarker of the defining neurodegeneration of PD.

2. Methods

2.1. Subjects and clinical test battery

This cross-sectional study involved 48 PD subjects (40 males, 8 females), mean age 69.4 ± 7.4 years (SD; range 56–84), mean Mini-Mental State Examination (MMSE) score of 28.4 ± 1.9 (22–30) and mean duration of disease of 8.4 ± 4.2 years (2.5–20) who participated in an imaging biomarker study of mobility impairments in PD and who completed the CHAMPS physical activity questionnaire at the time of study enrollment and imaging procedures. Subjects met the UK PD Society Brain Bank clinical diagnostic criteria. Abnormal striatal [^{11}C]DTBZ (DTBZ) PET findings were consistent with the diagnosis of PD in all subjects. No subjects had a history of a large artery stroke or other significant intracranial disease. Most subjects had moderate severity of disease: 1 patient in modified Hoehn & Yahr (HY) stage 1, 1 in stage 1.5, 6 in stage 2, 22 in stage 2.5, 14 in stage 3, 3 in stage 4 and 1 in stage 5. The mean HY stage was 2.7 ± 0.7. All subjects were treated with dopaminergic agents. Thirty-four subjects with PD were taking a combination of dopamine agonist and carbidopa–levodopa medications, 13 were using carbidopa–levodopa alone, 1 was taking dopamine agonist alone. All subjects completed the Unified PD Rating Scale (UPDRS). Mean LED was 973.0 ± 491.5 mg. Subjects on dopaminergic drugs were examined in the morning after withholding dopaminergic drugs overnight. Mean motor UPDRS score was 27.5 ± 10.3 (7–53). UPDRS motor scores were divided into sub-scores for tremor (UPDRS items 20 and 21), rigidity (item 22), distal appendicular bradykinesia (items 23–26 and 31), and axial symptoms (items 27–30).

The CHAMPS physical activity questionnaire was completed to assess levels of non-exercise and exercise physical activity levels [12]. The survey is designed specifically to be utilized by older adults, and has established reliability, sensitivity, and construct validity [12]. This questionnaire provides data on the duration, in hours per week, of various physical activities over a 4-week timeframe. Physical activity here comprises of a number of listed activities that older individuals and less active patients would be more likely to participate in, encompassing a combination of varying levels of vigorous physical activity (exercise), in addition to daily routine activities and recreational activities with physical components (non-exercise physical activity). Use of the CHAMPS questionnaire allows greater sensitivity to measure modest physical activity in this population that would be missed by physical activity scales focusing on more vigorous activities. Total physical activity levels were calculated, based on the standard scoring formula, as summed scores of CHAMPS questionnaire items 7, 9, 10, 14–16, and 19–40. Exercise activities, defined as more vigorous physical activity levels, were summed from items 7, 14–16, 19, 21, 23–26, 29–33, 36–38 and 40. Non-exercise physical activity levels were calculated by determining the difference between total and exercise physical activity scores. Non-exercise and exercise physical activity scores reflect total duration of physical activity in hours during a 4-week period. Supplemental Table 1 provides a listing of the individual demographic, clinical and CHAMPS activity data in the subjects.

The study was approved by the Institutional Review Boards of the University of Michigan and Ann Arbor VAAAHS. Written informed consent was obtained from all subjects prior to any research procedures.

2.2. Imaging techniques

All subjects underwent brain MRI and [^{11}C]DTBZ vesicular monoamine transporter type 2 (VMAT2) PET except for a single subject where the PET scan failed because of technical reasons. [^{11}C]DTBZ was prepared as described previously [13]. A bolus/infusion protocol was used for [^{11}C]DTBZ (15 mCi) in 60 min [14]. [^{11}C]DTBZ PET imaging was performed the morning after withholding dopaminergic medications overnight. The procedure was explained to the patients and the PET technologist ensured that they were laying properly and comfortably on the camera table to minimize movement. MRI was performed on a 3 T Philips Achieva system (Philips, Best, The Netherlands) and PET imaging was performed in 3D imaging mode with an ECAT Exact HR + tomograph (Siemens Molecular Imaging, Inc., Knoxville, TN) as reported previously [15].

2.3. Analysis

All image frames were spatially coregistered within subjects with a rigid-body transformation to reduce the effects of subject motion during the imaging session [16]. Interactive Data Language image analysis software (Exelis VIS, Inc., Boulder, CO) was used to manually trace volumes of interest (VOI) on MRI images to include caudate nucleus, and putamen of each hemisphere. Total

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