Parkinsonism and Related Disorders 23 (2016) 45–49

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Neuroimaging and clinical predictors of fatigue in Parkinson disease

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ARTICLE INFO

Article history:
Received 9 October 2015
Received in revised form
16 November 2015
Accepted 25 November 2015

Keywords:
Parkinson disease
Fatigue
PET imaging

ABSTRACT

Background: Fatigue is disabling in Parkinson disease. It is often associated with other non-motor symptoms, but little is known about its underlying pathophysiology.
Objective: To investigate neuroimaging (using dopaminergic and cholinergic PET) and clinical factors associated with fatigue severity in PD.
Methods: 133 PD subjects (96M/37F) completed the Fatigue Severity Scale, Movement Disorders Society-Sponsored Revision of the Unified PD Rating Scale (MDS-UPDRS), Hoehn-Yahr staging, validated scales for depression, anxiety, apathy, sleep, and cognition, and underwent [^{11}C]methyl-4-piperidinyl propionate (PMP) acetylcholinesterase (AChE) and [^{11}C]dihydrotetrabenazine (DTBZ) monoaminergic PET imaging. We explored contributions to PD fatigue using separate regression models based either on neuroimaging parameters or clinicometric scales.
Results: In a neuroimaging regression model, neither striatal DTBZ uptake nor AChE PMP uptake were predictors of fatigue in PD. In a post-hoc neuroimaging regression model, stratifying the total cohort into mild vs. moderate-to-severe PD, striatal DTBZ uptake was a significant predictor of fatigue in mild but not moderate-to-severe PD. In a clinicometric regression model, higher Beck Depression Inventory-somatic subscore, higher levodopa dose equivalents and younger age were all significant predictors of fatigue in PD, but the MDS-UPDRS non-motor experiences of daily living score was the best predictor overall.
Conclusions: Cholinergic uptake was not a predictor of fatigue in PD, but nigrostriatal dopaminergic denervation predicted fatigue in mild disease. Total non-motor symptom burden, somatic affective symptoms, levodopa dose equivalents, and younger age were independent clinical predictors of fatigue.

1. Introduction

Fatigue is a problem for up to 58% of Parkinson disease (PD) patients [1,2] and over half consider fatigue to be one of their 3 most disabling symptoms [2]. It is even present in early PD [3,4], and while most studies have found no significant association between fatigue and PD motor severity [1], some have reported significant correlations between increasing fatigue and increasing disease severity [5,6]. Fatigue has a negative impact on activities of daily living and quality of life in PD [3,6], and is commonly associated with other non-motor symptoms such as sleepiness, apathy, and depression [1], yet little is known about its underlying pathophysiologic mechanisms.

Levodopa treatment may partially improve fatigue [4,7], suggesting involvement of the dopaminergic system, but previous imaging studies have suggested that the degree of nigrostriatal denervation is not different between fatigued and non-fatigued PD patients [4,8]. Although dopaminergic denervation is a critical early step in PD pathophysiology, its presence does not fully explain the heterogeneity of PD clinical features, many of which develop or progress years after the onset of the disease. A sequential model of disease progression has been proposed where a predominant hypodopaminergic state marks the early clinical stage of PD with subsequent degeneration of extra-nigral non-dopaminergic systems as disease advances [9]. This emerging concept has great clinical implications as it is the non-dopaminergic symptoms that cause the greatest disability in the later stages of the disease [9,10].

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http://dx.doi.org/10.1016/j.parkreldis.2015.11.029
1353-8020/

Early dopaminergic losses have a robust association with appendicular motor impairment in PD, but also contribute to non-motor symptoms, including mild cognitive impairment, especially in the domain of executive function [11,12]. In later stages of PD, patients may develop levodopa unresponsive symptoms such as falls and dementia, which have been associated with cortical and subcortical cholinergic denervation and deposition of β-amyloid fibrillary plaques [11,13–15].

We hypothesized that both nigrostriatal dopaminergic and cholinergic denervation might contribute to fatigue in PD, because of involvement of the dopaminergic system early on in the disease and cholinergic dysfunction as the disease progresses. Because fatigue in PD is also associated with other non-motor symptoms, we also explored which clinical measures best predict fatigue.

2. Methods

2.1. Subjects

This cross-sectional study included 133 PD subjects (96 men/37 women) who were recruited from Movement Disorders Clinics at the University of Michigan and the Veteran Affairs Ann Arbor Health System (ClinicalTrials.gov Identifier:NCT01565473, NCT01106976). All subjects met UK PD Society Brain Bank Research Center clinical diagnostic criteria for PD [16] and completed [^{11}C] dihydrotetrabenazine (DTBZ) vesicular monoamine transporter type 2 (VMAT2) as well as [^{11}C] methyl-4-piperidinyl propionate (PMP) acetylcholinesterase (AChE) PET imaging. Subjects with MMSE scores <24 were not eligible, and subjects with diabetes mellitus were excluded from analysis because a history of diabetes represented a contraindication for an overlapping imaging study in the same cohort. Of the 133 subjects, 60 (45%) took carbidopa/levodopa only, 14 (11%) took a dopamine agonist, 48 (36%) took a combination of carbidopa/levodopa and a dopamine agonist, and 11 (8%) subjects did not take any PD medications. Twenty (15%) were on antidepressant drugs. No subjects were taking cholinesterase inhibitors or pure anticholinergic drugs.

2.2. Clinical assessments

Fatigue was measured by the Fatigue Severity Scale (FSS) [17], a 9 item, self-administered, fatigue scale. The items are brief and rated on a Likert scale from 1 “completely disagree” to 7 “completely agree”, and the average score of all 9 items represents the total FSS score. The FSS has shown high reliability, validity and internal consistency in both PD and non-PD populations [18].

Subjects also underwent clinical evaluation with Movement Disorders Society-revised Unified PD Rating Scale (MDS-UPDRS) [19], modified Hoehn-Yahr (H–Y), Epworth Sleepiness Scale (ESS) [20], Insomnia Severity Index (ISI) [21], Beck Depression Inventory (BDI) [22], State-Trait Anxiety Inventory (STAI) [23], the Marin Apathy Evaluation Scale (AES) [24], and a comprehensive neuropsychological test battery, which has been previously reported [25]. We computed somatic and affective BDI subscores to better distinguish somatic and affective elements that may underlie fatigue in PD. Composite z-scores were calculated for the different cognitive domains (memory, executive, attention and visuospatial functions) tested with the neuropsychological battery, based on normative data. A global composite z-score was calculated as the average of the four domain z-scores. The MDS-UPDRS, as well as imaging with the (+)-[^{11}C]DTBZ VMAT2 ligand, were conducted after withholding dopaminergic medications overnight followed by [^{11}C]PMP AChE ligand PET and brain magnetic resonance imaging (MRI).

2.3. Standard protocol approvals, registrations, and patient consents

The study was approved by the Institutional Review Boards of the University of Michigan. Written consent was obtained from all subjects.

2.4. Imaging techniques

Magnetic resonance imaging was performed using a 3 T Philips Achieva system (Philips, Best, The Netherlands) with an 8-channel head coil and the “ISOVOX” exam card protocol primarily designed to yield isotropic spatial resolution. A standard T1-weighted series of a 3D inversion recovery-prepared turbo-field-echo was performed in the sagittal plane using TR/TE/TI = 9.8/4.6/1041ms; turbo factor = 200; single average; field of view = 240 × 200 × 160 mm; acquired matrix = 240 × 200. 160 slices were reconstructed to 1 mm isotropic resolution. This sequence maximizes contrast among gray matter, white matter, and cerebrospinal fluid and provides high-resolution delineation of cortical and subcortical structures.

[^{11}C]PMP and [^{11}C]DTBZ PET Imaging were performed in 3D imaging mode using an ECAT HR + tomograph (Siemens Molecular Imaging, Inc., Knoxville, TN), which acquires 63 transaxial slices (slice thickness: 2.4 mm; intrinsic in-plane resolution: 4.1 mm full-width at half maximum over a 15.2 cm axial field-of-view. A NeuroShield (Scanwell Systems, Montreal, Canada) head-holder/shielding unit was attached to the patient bed to reduce the contribution of detected photon events originating from the body outside the scanner field-of-view. Prior to the DTBZ and PMP injections, a 5-min transmission scan was acquired using rotating ^{68}Ge rods for attenuation correction of emission data using the standard vendor-supplied segmentation and re-projection routines.

No-carrier-added (+)-[^{11}C]DTBZ (250–1000 Ci/mmol at the time of injection) was prepared as reported previously [26]. Dynamic PET scanning was performed for 60 min as previously reported [25]. [^{11}C]PMP was prepared in high radiochemical purity (>95%) by N-[^{11}C]methylation of piperidin-4-yl propionate using a previously described method [27]. Dynamic PET scanning was performed for 70 min as previously reported [25].

All image frames were spatially coregistered within subjects with a rigid-body transformation to reduce the effects of subject motion during the imaging session. Interactive Data Language image analysis software (Research systems, Inc., Boulder, CO) was used to manually trace volumes of interest on MRI images to include the thalamus, caudate nucleus, and putamen of each hemisphere. Total neocortical VOI were defined using semi-automated threshold delineation of the cortical gray matter signal on the magnetic resonance imaging scan.

AChE [^{11}C]PMP hydrolysis rates (k_3) in the thalamic and neocortical regions of interest were estimated using the striatal volume of interest (defined by manual tracing on the MRI scan of the putamen and caudate nucleus) as the tissue reference for the integral of the precursor delivery [28]. [^{11}C]DTBZ distribution volume ratio (DVR) was estimated using the Logan plot graphical analysis method with the striatal time activity curves as the input function and the total neocortex as reference tissue, a reference region overall low in VMAT2 binding sites, with the assumption that the non-displaceable distribution is uniform across the brain at equilibrium [29].

2.5. Data analysis

Stepwise multivariable linear regression analysis with FSS score