FEATURED ARTICLE

β-Amyloid and Postural Instability and Gait Difficulty in Parkinson's Disease at Risk for Dementia

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ABSTRACT: Although motor impairments in Parkinson's disease (PD) are attributed to nigrostriatal dopaminergic denervation, postural instability and gait difficulty (PIGD) features are less responsive to dopaminergic medications. PIGD features are a risk factor also for the development of dementia in PD (PDD). These observations suggest that nondopaminergic mechanisms may contribute to axial motor impairments. The aim was to perform a correlative PET study to examine the relationship between neocortical β-amyloid deposition ([^{11}C]-Pittsburgh Compound B), nigrostriatal dopaminergic denervation ([^{11}C]-dihydrotetrabenazine), and PIGD feature severity in PD patients at risk for dementia. This was a cross-sectional study of 44 PD patients (11 female and 33 male; 69.5 ± 6.6 years of age; 7.0 ± 4.8 years motor disease duration; mean H & Y stage: 2.7 ± 0.5) who underwent PET, motor feature severity assessment using the *Movement* Disorder Society revised UPDRS, and the Dementia Rating Scale (DRS). Linear regression (R^2_{adj} = 0.147; $F_{4,39}$ = 2.85; P = 0.036) showed that increased PIGD feature severity was associated with increased neocortical [^{11}C]-Pittsburgh Compound B binding (β = 0.346; t_{39} = 2.13; P = 0.039) while controlling for striatal [^{11}C]-dihydrotetrabenazine binding, age, and DRS total score. Increased neocortical β-amyloid deposition, even at low-range levels, is associated with higher PIGD feature severity in PD patients at risk for dementia. This finding may explain why the PIGD motor phenotype is a risk factor for the development of PDD. © 2012 *Movement* Disorder Society

Key Words: Parkinson's disease; β-amyloid; dopamine; PET; MDS-UPDRS

Postural instability and gait difficulty (PIGD) features are among the most disabling motor features of Parkinson's disease (PD) and are least responsive to dopaminergic medications.[1,2] There is a need to explore nondopaminergic mechanisms of PIGD, because the presence of PIGD features is a critical determinant of quality of life in PD.[3,4]

PD is a multisystem neurodegeneration syndrome manifesting with both motor and cognitive morbidity. There are several lines of evidence showing an intrinsic association between cognition and mobility in PD. First, the PIGD motor subtype is a risk factor for the development of dementia in PD (PDD).[5–7] Second, walking and/or maintaining upright balance is affected by concurrent cognitive tasks.[8] Third, cognitive impairment is a risk factor for falls.[9] Although some aspects of cognitive dysfunction are related to striatal dopaminergic deficits,[10] dopamine (DA) replacement therapy has mixed effects on cognition in PD.[11,12] Given the ambiguous role of DA in the etiology of both PIGD features and cognitive impairment, nondopaminergic processes may underlie the relationship between cognition and PIGD features in PD.

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In Alzheimer's disease (AD), deposition of β-amyloid (Aβ) plaques occurs early in disease[13] and is associated with cognitive impairment.[14] Postmortem findings of Alzheimer's pathology are found also in the brains of PD patients, typically reflecting late-stage (and age-related) pathology.[15] However, *in vivo* imaging studies of Aβ using ^{11}C-Pittsburgh compound-B ([^{11}C]-PiB) PET generally show lower, more-variable levels of Aβ in the neocortex of subjects with PD or PDD, when compared to AD.[16–20] The effect of neocortical Aβ on clinical features of PD, particularly with respect to DA nonresponsive motor symptoms, has not been well studied. Given the severe striatal dopaminergic deficits of PD, it is possible that comorbid Aβ pathology may aggravate specific clinical features of PD.

The aim of this study was to examine the relationship between neocortical Aβ burden, estimated *in vivo* with [^{11}C]-PiB, and ratings of PIGD features in PD patients with mild cognitive impairment or with other dementia risk factors. The effect of nigrostriatal dopaminergic denervation on these features was taken into account by *in vivo* [^{11}C]-DTBZ PET imaging of the vesicular monoaminergic transporter, type 2. We hypothesized that increased neocortical [^{11}C]-PiB retention is associated with increased PIGD feature severity.

Patients and Methods

Subjects

This cross-sectional study included 44 PD patients with either mild cognitive impairment symptoms or known risk factors for developing PD-associated dementia, specifically older age, longer disease duration, or evidence of PIGD features.[6,21,22] These patients underwent a [^{11}C]-PiB scan as part of a larger ongoing cohort study (National Institutes of Health P01 NS015655). Detailed demographic and disease severity information is provided in Table 1.

Patients met the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria.[23] The diagnosis of PD was confirmed by the presence of a typical pattern of nigrostriatal dopaminergic denervation on [^{11}C]-DTBZ PET imaging.[24]

All subjects were on DA replacement therapy (see also Table 1). None of the subjects were on anticholinergic or cholinesterase inhibitor drugs. Subjects were clinically examined and imaged in the morning after overnight withholding of their dopaminergic drugs.

Written informed consent was obtained from all subjects before research procedures. The University of Michigan Medical School Institutional Review Board (Ann Arbor, MI) for human studies approved the study.

Clinical Assessments

Clinical evaluations included PD motor feature assessment using the *Movement* Disorder Society revised UPDRS (MDS-UPDRS).[25,26] The PIGD score was calculated as the sum of items 2.11 to 2.13 and 3.9 to 3.13, and a non-PIGD score was calculated as the sum of the non-PIGD items of parts II and III of the MDS-UPDRS. Cognitive capacity was assessed with the Dementia Rating Scale (DRS)[27] with subjects on their regular dopaminergic medications.

TABLE 1. Detailed demographic information, modified H & Y staging,[46] and medication use, including levodopa equivalent dose[47] in milligrams (mg)

Gender	
Female	N = 11
Male	N = 33
Age, years	69.5 ± 6.6 (55–84)
Motor disease duration, years	7.0 ± 4.8 (1–20)
Modified H & Y staging	2.7 ± 0.5
1.5	N = 1
2.0	N = 3
2.5	N = 23
3.0	N = 14
4.0	N = 3
Dopaminergic medication use	
CL	N = 23
DA agonist	N = 6
Combination CL and DA agonist	N = 15
Levodopa equivalent dose (mg)	812.4 ± 630.3 (100–3,180)

Values represent mean ± standard deviation (range). Abbreviation: CL, carbidopa-levodopa.

MRI

All subjects underwent brain MRI for anatomic coregistration with PET. MRI was performed on a 3 T Philips Achieva system (Philips, Best, The Netherlands) utilizing an eight-channel head coil and the "ISOVOX" exam card protocol primarily designed to yield isotropic spatial resolution. A standard T1-weighted series of a three-dimensional (3D) inversion recovery-prepared turbo field echo was performed in the sagittal plane using the following: repetition time/echo time/inversion time = 9.8/4.6/1041 ms; turbo factor = 200; single average; field of view = 240 × 200 × 160 mm; and acquired matrix = 240 × 200. One hundred and sixty slices were reconstructed to 1-mm isotropic resolution.

PET Imaging

PET imaging was 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, Quebec, 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. Before the radioligand injections, a 5-minute transmission scan was acquired using rotating ^{68}Ge rods for attenuation correction of emission data using the standard vendor-supplied segmentation and reprojection routines.

[^{11}C]-DTBZ (no-carrier-added (+)-α-[^{11}C]-dihydrotetrabenazine) was prepared as reported previously.[28] [^{11}C]-DTBZ PET scans were performed using a bolus/infusion protocol acquiring 15 emission scans over 60 minutes (4 × 30 seconds; 3 × 1 minute; 2 × 2.5 minutes; 2 × 5 minutes; and 4 × 10 minutes), with a priming bolus of 55%, followed by continuous infusion of the remaining 45% over the study duration using a dose of 555 MBq.

[^{11}C]-PiB (*N*-methyl-[^{11}C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole; Pittsburgh Compound B) was synthesized following published methods.[29,30] [^{11}C]-PiB PET scans were performed using a bolus/infusion protocol acquiring 17 emission scans over 80 minutes (same as [^{11}C]-DTBZ scan sequence plus two additional 10-minute scans), with a priming bolus of 40%, followed by continuous infusion of the remaining 60% over the study duration using a dose of 666 MBq.

All subjects were studied supine, with eyes and ears unoccluded, resting quietly in a dimly lit room.

PET Analysis

All dynamic PET imaging frames were spatially coregistered within subjects with a rigid body transformation to reduce the effects of subject motion during the imaging session.[31] These motion-corrected PET frames were spatially coregistered to the MRI using *SPM8* software (Wellcome Trust Center for Neuroimaging, London, UK). *IDL* image-analysis software (Research Systems, Inc., Boulder, CO) was used to manually trace volumes of interest (VOIs) on the MRI scan. Traced VOIs included the striatum (caudate and putamen), thalamus, cerebellum, and the neocortex. Neocortical VOI definition used semiautomated thresholding delineation of the neocortical gray-matter signal on MRI images.

Time-activity curves for each VOI were generated from the spatially aligned PET frames. [^{11}C]-PiB and [^{11}C]-DTBZ PET distribution volume ratio (DVR), a measure of binding, was estimated by using Logan's plot graphical analysis method,[32] with the time-activity curves as the input function and the cerebellar gray matter as reference tissue for [^{11}C]-PiB and the neocortex as reference tissue for [^{11}C]-DTBZ.

Statistical Analysis

Variables were rank-order transformed to mitigate the effect of possible outliers. Linear regression analysis was performed to assess the association between PIGD subscore and neocortical [^{11}C]-PiB DVR while controlling for striatal [^{11}C]-DTBZ DVR, age, and DRS total score. Post-hoc analyses were performed to assess the effects of subcortical [^{11}C]-PiB DVR on PIGD subscore. Analyses were performed using *PASW Statistics 18* (IBM, Chicago, Ill).

TABLE 2. Mean ± standard deviation (range) for DRS, MDS-UPDRS summed PIGD and non-PIGD subscores, and PET ligands

DRS (0–144)	136.4 ± 5.0 (123–144)
MDS-UPDRS	
Motor Aspects of Experiences of Daily Living (0–52)	10.6 ± 5.9 (2–26)
Motor Examination (0–132)	37.8 ± 14.6 (14.5–69.5)
PIGD subscore (0–32)	9.0 ± 4.9 (1.5–27.0)
non-PIGD subscore (0–152)	39.4 ± 14.2 (18.0–72.5)
PET	
Striatal [^{11}C]-DBTZ DVR	1.90 ± 0.31 (1.50–2.94)
Neocortical [^{11}C]-PiB DVR	1.16 ± 0.16 (0.93–1.78)
Thalamic [^{11}C]-PiB DVR	1.54 ± 0.13 (1.19–1.80)
Striatal [^{11}C]-PiB DVR	1.37 ± 0.19 (1.07–2.10)

Results

Descriptive results for the MDS-UPDRS, DRS, and PET ligands are presented in Table 2. Subjects had mild to moderate motor disease severity and a mean DRS total score that was within the mildly impaired range.[33] Across all subjects, neocortical [^{11}C]-PiB binding was generally in the low range, but regionally more elevated in the frontal and temporal lobes and the cingulate gyrus (Fig. 1).

Linear regression analysis showed that neocortical [^{11}C]-PiB binding ($\beta = 0.346$; $t_{39} = 2.13$; $P = 0.039$) significantly predicted MDS-UPDRS PIGD subscore ($R^2_{adj} = 0.147$; $F_{4,39} = 2.85$; $P = 0.036$; Fig. 2), whereas there were no significant effects of striatal [^{11}C]-DTBZ binding ($\beta = -0.232$, $t_{39} = -1.52$; $P = 0.136$), age ($\beta = 0.125$; $t_{39} = 0.85$; $P = 0.400$), or DRS total score ($\beta = 0.100$; $t_{39} = 0.62$; $P = 0.538$). Additional linear regression analysis showed that the non-PIGD subscore could not be significantly predicted by the same independent variables ($R^2_{adj} = 0.072$; $F_{4,39} = 1.84$; $P = 0.142$). Reanalysis with possible influential outliers removed (see also Fig. 2) resulted in the same findings (results not shown).

Post-hoc linear regression analyses were performed to examine possible effects of subcortical [^{11}C]-PiB binding on PIGD subscore. These analyses showed that neither striatal [^{11}C]-PiB binding nor thalamic [^{11}C]-PiB binding significantly predicted PIGD subscores while controlling for striatal [^{11}C]-DTBZ binding, age, and DRS total score (results not shown).

Discussion

We examined the relationship between PIGD feature severity and neocortical Aβ burden in PD patients

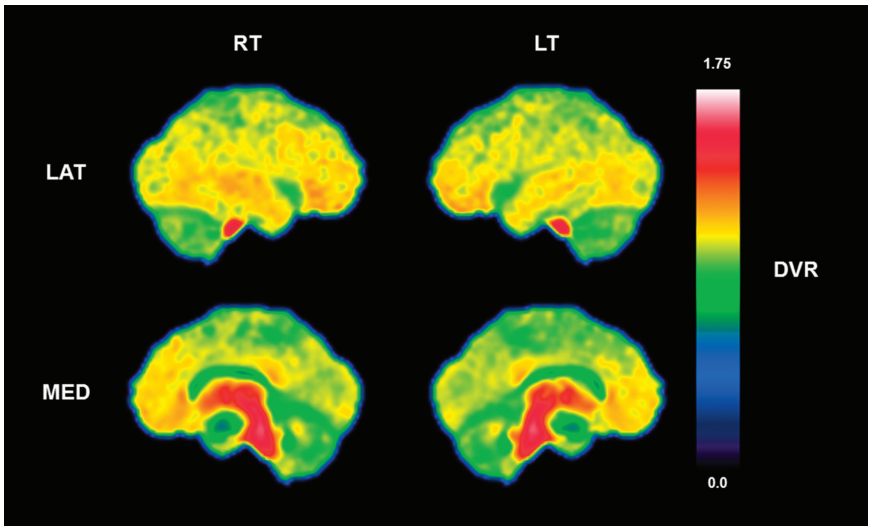

FIG. 1. Parametric lateral and medial projections of [^{11}C]-PiB binding averaged across all 44 subjects. Overall, there was low-range binding; however, regionally increased binding was observed in the cingulate gyrus as well as temporal and frontal lobes. There was high nonspecific white-matter [^{11}C]-PiB binding in the brainstem and thalamus. RT, right; LT, left; LAT, lateral; MED, medial.

with mild cognitive impairment or at risk for development of dementia. We found that increased PIGD feature severity was associated with increased neocortical Aβ burden while controlling for the effect of possible confounding variables, such as the degree of striatal dopaminergic denervation, age, or the degree of cognitive capacity impairment. This was a PIGD feature-specific effect, because neocortical Aβ burden did not have an association with non-PIGD feature severity. Furthermore, the results remained significant even after the exclusion of subjects with more-severe neocortical amyloidopathy. Subcortical Aβ burden did not affect PIGD feature severity.

Dopaminergic denervation is severe in PD, even at the onset of the disease.[24,34] For example, Frey et al. have reported on reductions of striatal dopaminergic [^{11}C]-DTBZ binding of 61% in the putamen and 43% in the caudate nucleus, with no overlap in putamen [^{11}C]-DTBZ binding between individual elderly controls and PD patients.[34] In our study, striatal [^{11}C]-DTBZ DVR was in the same range. The results of this study support our hypothesis that in the

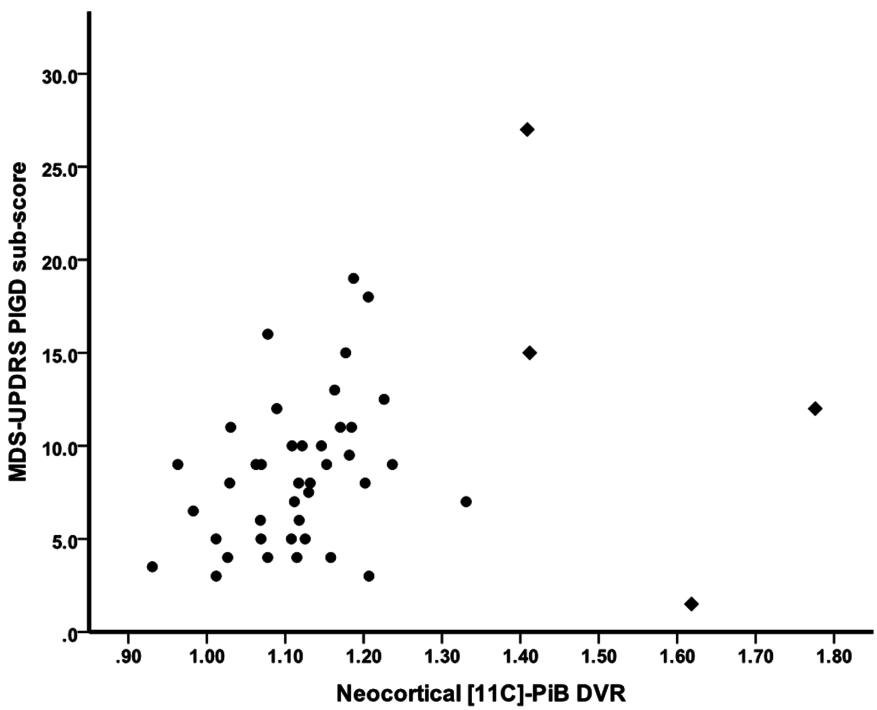

FIG. 2. Scatterplot of neocortical [^{11}C]-PiB binding against PIGD subscore across all subjects. Possible influential outliers are identified by diamonds.

presence of severe striatal dopaminergic denervation, comorbid neocortical amyloidopathy may have exacerbating effects on gait and postural stability, even when the amyloidopathy is at below-AD level of Aβ-binding levels.[35] This suggests that relatively low levels of comorbid neocortical Aβ plaques are of pathophysiological significance in PD and may aggravate motor impairments of PD patients.

Further evidence for a possible role of cortical amyloidopathy on the etiology of balance and gait impairments can be found in AD patients. Subtle changes in balance and gait occur early in the course of AD.[36] Several studies have shown that gait and static standing balance characteristics of AD patients are different from healthy subjects.[37–39] These changes are especially evident when there are additional cognitive task demands while walking.[40–42] These observations support an intrinsic relationship between cognition and motor control functions and suggest a possible pathogenic role for neocortical amyloidopathy in gait dysfunction.

The cross-sectional study design and regression analyses were limitations of our study, because these do not allow for causal assessment of the relationship between PIDG feature severity and the degree of neocortical amyloidopathy. Prospective studies are needed to confirm that amyloidopathy is an important mechanism underlying both progression of PIGD motor features and cognitive decline in PD.

PD is a multisystem neurodegenerative disorder.[43] Our study shows that, in the presence of severe nigrostriatal dopaminergic denervation, even relatively low levels of comorbid neocortical amyloidopathy may augment gait and postural impairments in PD. These results and our recent findings of an association between cortical amyloidopathy and the degree of cognitive impairment in PD patients[44] suggest that cortical amyloidopathy may provide a common mechanism for PIGD features and cognitive impairment. This may explain why the PIGD motor phenotype is a risk factor for the development of PDD. Several promising therapies have been tested in AD patients that target Aβ production, aggregation, or accumulation, which, likely, are most effective when applied to asymptomatic patients with very early signs of AD pathology.[45] Future studies could evaluate whether early treatment of amyloidopathy may modify the progression of PIGD features in PD.

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