In vivo amyloid imaging in autopsy-confirmed Parkinson disease with dementia

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ABSTRACT

Objective: To investigate the specificity of in vivo amyloid imaging with [^{11}C]–Pittsburgh Compound B (PIB) in Parkinson disease dementia (PDD).

Methods: We performed detailed neuropathologic examination for 3 individuals with PDD who had PIB PET imaging within 15 months of death.

Results: We observed elevated cortical uptake of [^{11}C]-PIB on in vivo PET imaging in 2 of the 3 cases. At autopsy, all 3 individuals had abundant cortical Lewy bodies (Braak PD stage 6), and were classified as low-probability Alzheimer disease (AD) based on NIA-Reagan criteria. The 2 PIB-positive individuals had abundant diffuse Aβ plaques but only sparse neuritic plaques and intermediate neurofibrillary tangle pathology. The PIB-negative individual had rare diffuse plaques, no neuritic plaques, and low neurofibrillary tangle burden.

Conclusions: [^{11}C]–Pittsburgh Compound B (PIB) PET is specific for fibrillar Aβ molecular pathology but not for pathologic diagnosis of comorbid Alzheimer disease in individuals with Parkinson disease dementia. The ability to specifically identify fibrillar Aβ amyloid in the setting of α-synucleinopathy makes [^{11}C]-PIB PET a valuable tool for prospectively evaluating how the presence of Aβ amyloid influences the clinical course of dementia in patients with Lewy body disorders. ***Neurology***® **2010;74:77–84**

GLOSSARY

AD = Alzheimer disease; **BP** = binding potentials; **CDR** = Clinical Dementia Rating; **DAT** = dementia of the Alzheimer type; **DLB** = dementia with Lewy bodies; **DV** = distribution volume; **MMSE** = Mental State Examination; **NPI-Q** = Neuropsychiatric Inventory Questionnaire; **PDD** = Parkinson disease dementia; **PIB** = Pittsburgh Compound B; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Individuals with Parkinson disease (PD) are nearly 6 times more likely to develop dementia than age-matched controls, and the majority of individuals with PD who survive more than 15 years after diagnosis will develop dementia.[1,2] Clinicopathologic investigations have revealed heterogeneous histopathology, with Alzheimer disease (AD) pathology (amyloid plaques and neurofibrillary tangles) present in a subset of individuals with PD dementia (PDD).[1] When present, AD pathology is typically found in conjunction with other neuropathologic changes, including limbic and cortical Lewy bodies and degeneration of subcortical monoaminergic and cholinergic pathways. The contribution of AD pathology to the pathogenesis of dementia in the setting of PD is thus uncertain. The presence of AD pathology has been postulated to influence clinical manifestations of dementia, for example masking features of dementia with Lewy bodies (DLB) such as hallucinations and fluctuations[3,4] or influencing the timing of dementia onset in patients with Lewy body disorders.[5]

Antemortem evaluation of Aβ plaque burden by PET imaging using amyloid-specific radiotracers can potentially clarify the role of these lesions in the pathogenesis of Lewy body–associated dementias (PDD and DLB). The tracer N-methyl-[^{11}C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole (or [^{11}C]-PIB for Pittsburgh Compound-B) has shown great promise for this purpose, demonstrating rapid diffusion across the blood–brain barrier, high affinity to a

Supplemental data at www.neurology.org

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single binding site on synthetic Aβ (Kd = 4.7 nM), and high affinity to a single binding site in homogenates of frontal cortex from brains with AD (Kd = 1.4 nM).[6,7] PET images of [^{11}C]-PIB in individuals with dementia of the Alzheimer type (DAT) reveal widespread increased tracer uptake in neocortical regions, with relative sparing of the occipital and sensory/motor cortices and minimal uptake in the cerebellar cortex.[8]

In an ongoing cohort study, we have performed [^{11}C]-PIB PET imaging in individuals with Lewy body disorders (including cognitively normal PD, PDD, and DLB) followed by longitudinal clinical and psychometric assessments. All enrolled participants have consented to postmortem neuropathologic evaluation. Our preliminary results, reported previously in abstract form, are consistent with findings of other investigators,[9-11] with a subset of individuals with Lewy body disorders (~20%) demonstrating elevated cortical [^{11}C]-PIB uptake.[12] We report here the postmortem neuropathologic findings for 3 individuals with PDD who had in vivo [^{11}C]-PIB PET imaging and subsequently had autopsy.

METHODS

Standard protocol approvals, registrations, and patient consents. All study procedures were approved by Washington University's Human Research Protection Office. Prior to enrollment, written informed consent was obtained for all participants. For individuals lacking capacity due to dementia, a surrogate decision-maker (spouse, first-degree family member, or health care proxy) provided informed consent and ongoing assent was obtained from the participant throughout the study procedures.

Subject selection and clinical assessment. Individuals were recruited from the greater St. Louis area; there were no gender or race restrictions. Participants with clinically probable or definite idiopathic PD (modified United Kingdom PD Brain Bank criteria[13]) or DLB[14] were screened via detailed clinical history (including review of motor, cognitive, and neuropsychiatric symptoms, comorbid medical conditions, and medications) and neurologic examination. Exclusionary criteria included other conditions that could contribute substantially to the subject's motor and/or cognitive impairment, including neurologic (e.g., Parkinson-plus disorders other than DLB), psychiatric (e.g., major affective disorders, unless cognitive impairment and mood symptoms were clearly temporally dissociated), or medical conditions (e.g., drug-induced or other delirium). From October 2006 to March 2009, we enrolled 10 healthy elderly control individuals and 40 individuals with iPD or DLB. Three of the enrolled participants subsequently died and donated their brains for the study.

All 3 of the deceased participants met clinical diagnostic criteria for PDD[1]; none had a known family history of dementia or PD. Individual histories are provided in appendix e-1 on the *Neurology*® Web site at www.neurology.org, and clinical data are summarized in table 1. Motor symptoms were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) subscale 3 (motor subscale) and Hoehn-Yahr staging while having benefit from medication (ON state). Levodopa equivalent daily dose was calculated using the following corrections: dose levodopa in sustained release form × 0.75; dose of levodopa taken with catechol-O-methyltransferase inhibitor × 1.3. None of the 3 participants reported here took a dopamine agonist or monoamine oxidase inhibitor at the time of the evaluation.

Severity of dementia was staged according to the Clinical Dementia Rating (CDR).[15] Impairment of function in 6 domains (memory, orientation, judgment and problem solving, community affairs, home and hobby, and personal care) is rated on a 0–3 scale (0 = normal; 1 = mild; 2 = moderate; 3 = severe). Global (weighted average) and sum CDR ratings are presented. Other standardized assessments included Mini-Mental State Examination (MMSE[16]), Neuropsychiatric Inventory Questionnaire (NPI-Q[17]), and Mayo Fluctuations scale.[18]

In vivo amyloid imaging. [^{11}C]-PIB was synthesized according to published methods.[19] PET imaging was performed using a Siemens 961 HR ECAT PET scanner (CTI, Knoxville, TN). Approximately 12 mCi of radiotracer (range, 10.4–14.5; specific activity ≥1,200 Ci/mmol) was injected via an antecubital vein, and a 60-minute, 3-dimensional (septa retracted) dynamic PET scan was collected. Images were reconstructed as 5-minute frames using scatter correction and a ramp filter. Frames were corrected for head motion using in-house software, and coregis-

Table 1 Clinical data

Case no. (gender)	Duration of motor impairment, y	Duration of cognitive impairment, y	UPDRS3 (ON)	H-Y stage	LEDD, mg	MMSE	CDR Global	CDR Sum of boxes	NPI-Q	Mayo fluct.
1 (M)	18	4	40	4	1,260	23	2	12	20	2
2 (F)	17	10	35	4	600	11	2	14	24	4
3 (M)	19	5	35	2	1,115	24	1	7	20	4

UPDRS3 = Unified Parkinson's Disease Rating Scale (motor subscale, maximum 108) during ON medication state; H-Y = Hoehn and Yahr stage; LEDD = levodopa equivalent daily dose; MMSE = Mini-Mental State Examination score (maximum score 30); CDR Global = Clinical Dementia Rating global score (0 = cognitively normal; 0.5 = very mild dementia; 1 = mild dementia; 2 = moderate dementia; 3 = severe dementia); CDR Sum = sum of individual ratings for 6 domains of cognitive function (maximum score 18); NPI-Q = Neuropsychiatric inventory questionnaire (maximum score 39); Mayo Fluct. = Mayo fluctuations score (maximum score 4).

tered to the patient's T1-weighted magnetization-prepared rapid gradient echo magnetic resonance scan obtained the same day. For visual display, the data from 30 to 60 minutes after radiotracer injection were summed, Gaussian filtered (full width half-maximum = 6 mm), and normalized to average brainstem intensity values.

For quantitative analyses, 3-dimensional regions of interest (prefrontal cortex, gyrus rectus, lateral temporal cortex, precuneus, occipital lobe, caudate nucleus, brainstem, and cerebellum) were created for each subject based on their individual MRI scans, with boundaries defined as previously described.[20] Time-activity curves were analyzed using Logan graphical analysis, with the cerebellum (which has minimal specific binding due to low Aβ plaque content) as the reference tissue input function.[20,21] Binding potentials (BP) were calculated from the tracer distribution volume (DV, reflected in the slope of the Logan graphical analysis) as BP = DV − 1. Mean cortical binding potentials were calculated for each subject as the average of all cortical regions except occipital lobe (which typically has lower Aβ plaque burden, even in advanced AD). For comparison, published mean values of MCBP calculated using identical methods are 0.63 in DAT and 0.09 in age-matched controls[20]; values greater than 0.2 are associated with low CSF Aβ_{42} levels[22] and are considered abnormally elevated.

Neuropathology. Brains were fixed in 10% neutral buffered formalin for 2 weeks, paraffin wax-embedded, and sections cut at 6 μm. Blocks were taken from frontal, temporal, parietal, and occipital lobes, thalamus, striatum including the nucleus basalis of Meynert, amygdala, hippocampus, midbrain, pons, medulla oblongata, and the cervical spinal cord. Histologic stains included hematoxylin and eosin and modified Bielschowsky silver impregnation. Immunohistochemistry was performed using the following antibodies: Aβ (10D5, Elan Pharmaceuticals, San Francisco, CA), phosphorylated tau (PHF-1, supplied by Dr. Peter Davies, Albert Einstein Medical School, Bronx, NY), ubiquitin (Dako, Glostrup, Denmark), α-synuclein (LB-509, Zymed, CA), and TDP-43 (Proteintech, Inc., Chicago, IL). Amyloid and tau burden was scored semiquantitatively in each of the sampled regions (0 = none; 1 = few/mild; 2 = moderate; 3 = severe); α-synucleinopathy with Lewy bodies was rated according to the scheme proposed by McKeith et al.[14] where 0 = none; 1 = <1 Lewy body per × 10 microscopic field; 2 = 1–3 Lewy bodies; 3 = 4–10 Lewy bodies; and 4 = >10 or numerous Lewy bodies.

RESULTS

In vivo amyloid imaging. Images representing the distribution of [^{11}C]-PIB PET activity from 30 to 60 minutes after tracer injection are shown in figure 1. Images from a 77-year-old female control participant without neurologic disease are displayed for comparison. Visual inspection revealed high signal in multiple cortical areas for 2 patients (case 1 and case 2), with relative sparing of primary sensorimotor and visual cortex. This pattern was highly similar to that previously described for patients clinically diagnosed with DAT.[8,22,23] In contrast, case 3 and the control participant showed uptake predominantly in white matter regions. This likely reflects nonspecific retention, as a recent study showed that PIB binding to white matter homogenates is nonsaturable.[24]

Binding potentials for selected regions of interest and mean cortical binding potentials for the 3 individuals are presented in table 2. Cases 1 and 2 had elevated PIB binding potentials in multiple cortical regions, with relative sparing of the occipital cortex. Case 1 also had elevated binding in the caudate nucleus. In contrast, case 3 had binding potentials near zero for all regions.

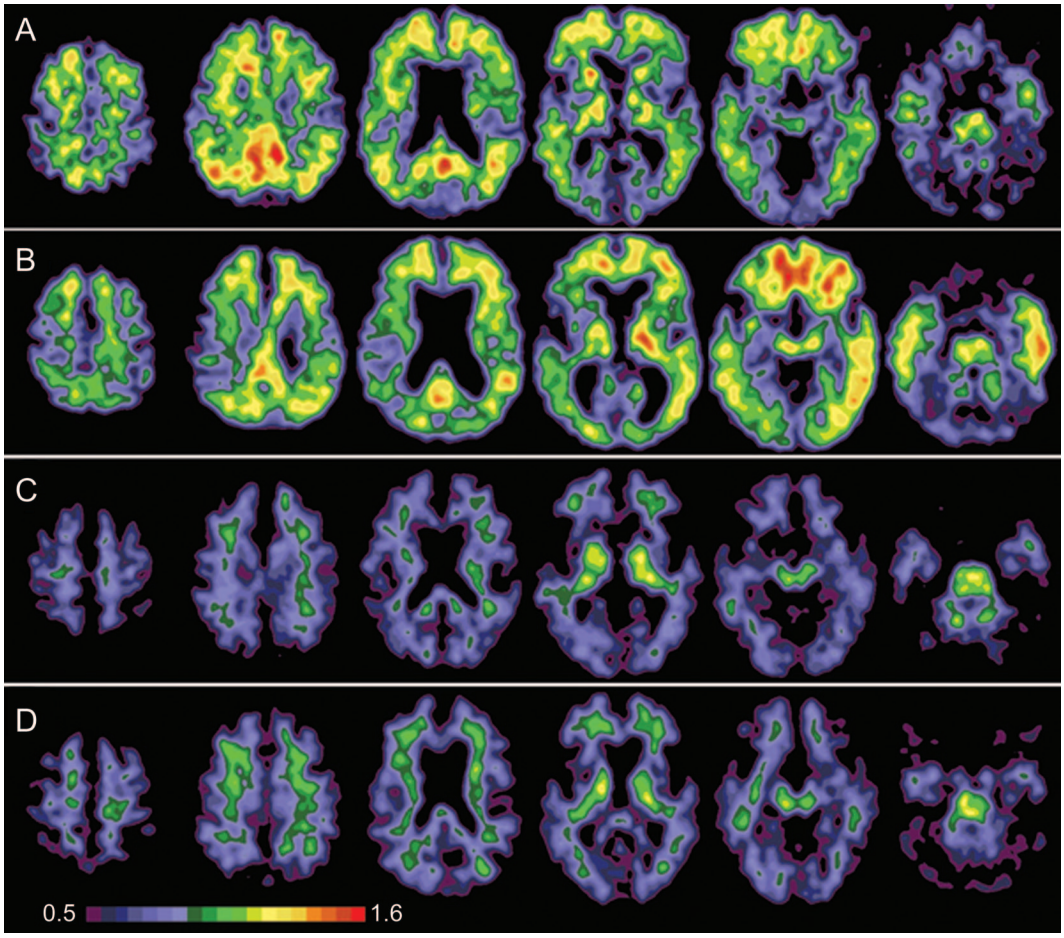
Neuropathology. Macroscopic findings included mild frontal, temporal, and parietal atrophy and dilatation of the lateral ventricles (less in case 3 than in cases 1 and 2), and normal hippocampal size in all 3 cases. As expected, there was pronounced loss of pigment in the substantia nigra (see representative images in figure e-1 on the *Neurology*® Web site at www.neurology.org).

Histologic findings for case 2 are illustrated in figure 2. In the substantia nigra, there was neuronal loss, extracellular pigment, gliosis, Lewy bodies, and Lewy neurites (figure 2, B and C). The parahippocampal gyrus contained abundant Lewy bodies (figure 2D) and moderate neurofibrillary tangle pathology (figure 2G). Extensive Aβ deposits in the frontal lobe were evident by immunohistochemistry (figure 2A); there was also cerebral amyloid angiopathy in leptomeningeal vessels.

Regional semiquantitative assessments of Aβ, tau, and α-synuclein burden for the 3 cases are presented in table 3. All 3 cases had abundant Lewy bodies in multiple neocortical and limbic regions. Cases 1 and 2 also had a high burden of Aβ plaque pathology (Braak amyloid stage C[25]), predominantly in the form of diffuse plaques. Although a few isocortical neurofibrillary tangles were seen in these 2 cases, they were very sparse and thus overall neurofibrillary tangle burden was rated as limbic stage (Braak NFT stage III[26]). In contrast, case 3 had minimal Aβ plaques (Braak amyloid stage A), and only sparse transentorhinal and entorhinal neurofibrillary tangles (Braak NFT stage I). Cerebral amyloid angiopathy was mild in case 1 and absent in the other 2 cases. Modest vascular pathology in the form of arteriolosclerosis was also a feature of all 3 brains (not shown). There were no infarcts in any of the 3 cases.

The presence of Lewy bodies in brainstem, limbic, and neocortical areas was consistent with PD stage 6 (range: 0–6) in all 3 cases.[27] The density and distribution of these lesions was also sufficient to meet "high probability" criteria for dementia with Lewy bodies[14]; because the parkinsonism preceded the cognitive changes by more than 1 year, the entity which describes these clinicopathologic features is called PDD rather than DLB.[1] In cases 1 and 2, the numerous neocortical Aβ plaques were sufficient for neuropathologic diagnosis of AD by Khachaturian

Figure 1 [^{11}C]-PIB PET images



(A) Case 1. (B) Case 2. Increased signal is evident in multiple cortical areas in these 2 individuals, including orbitofrontal and prefrontal cortex, precuneus, and temporal lobes. (C) Case 3. (D) Control participant. These 2 individuals have minimal PIB signal in cortical areas. PIB retention in white matter areas is likely due to nonspecific binding (see text).

criteria,[28] but the modest numbers of neuritic plaques and neocortical tangles were only sufficient to fulfill the criteria for "possible" AD according to Consortium to Establish a Registry for Alzheimer's Disease criteria,[29] and there was only a "low likelihood" that the cognitive changes are caused by AD according to the NIA-Reagan Institute criteria.[30] No other neurodegenerative diseases were identified in any of the three cases.

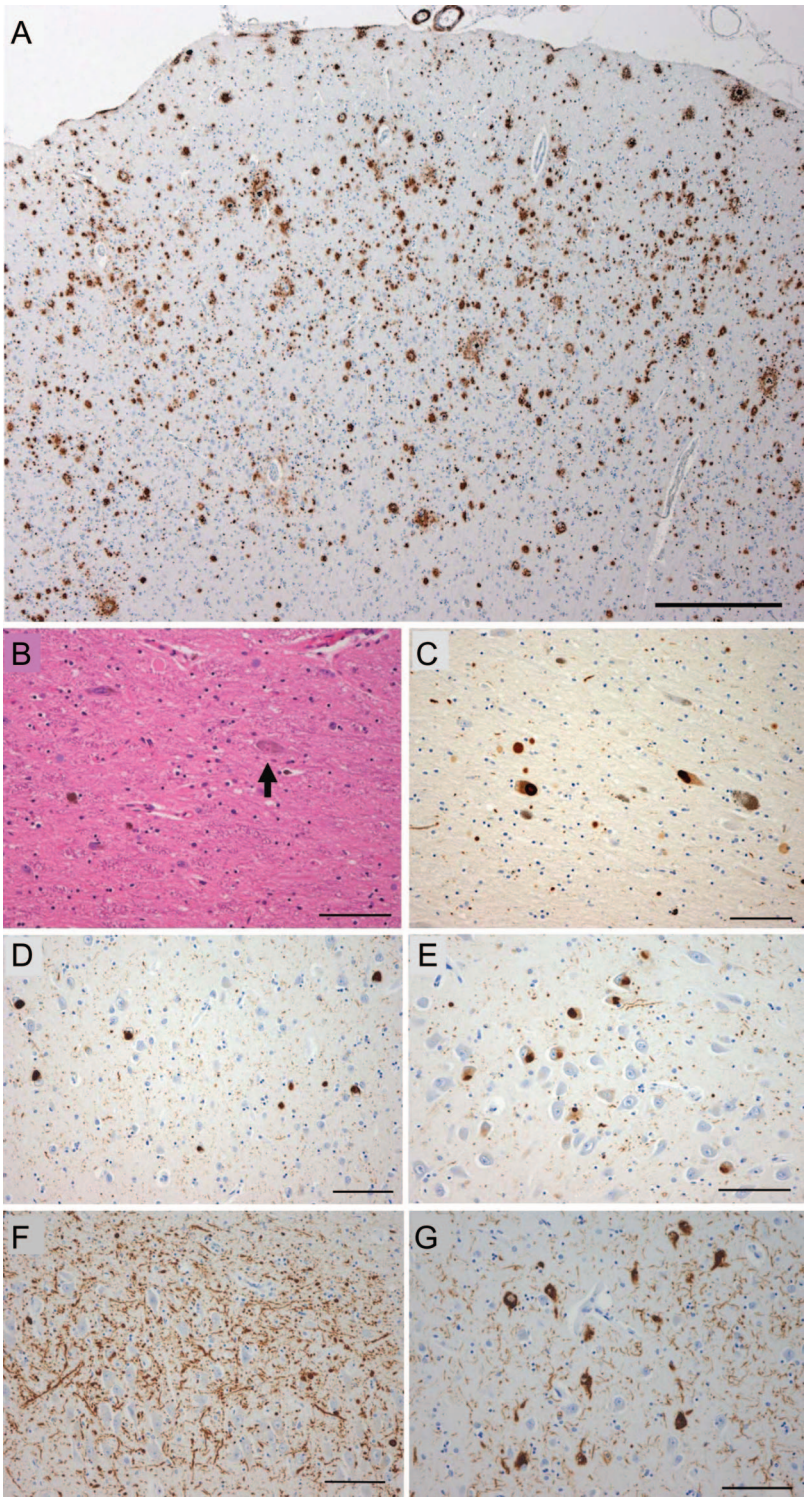
Table 2 Regional and mean cortical binding potentials (unitless ratio)[a]

	Case 1	Case 2	Case 3
Prefrontal cortex (A)	0.49	0.33	−0.08
Temporal cortex (B)	0.40	0.35	−0.02
Precuneus	0.68	0.41	0.00
Gyrus rectus	0.45	0.47	−0.11
Occipital cortex (C)	0.12	0.19	0.04
Caudate nucleus (D)	0.47	0.04	−0.21
Mean cortical binding potential	0.50	0.39	−0.05

[a]Letters in parentheses are provided for cross-referencing to the corresponding regions sampled for histopathologic evaluation (see table 3).

DISCUSSION The absence of elevated cortical [^{11}C]-PIB binding in an individual with PDD who had abundant cortical Lewy bodies and minimal cortical amyloid plaque pathology underscores the specificity of this tracer for fibrillar Aβ amyloid in in vivo imaging. Previous in vitro studies have demonstrated that PIB does not demonstrate specific binding to Lewy bodies (an amyloid composed of fibrillar α-synuclein[31]) in cortex homogenates from patients with Lewy body dementia lacking Aβ plaque, or to synthetic α-synuclein aggregates.[32] Our postmortem evaluation of individuals who underwent amyloid imaging strongly supports the notion that PIB PET is specific for Aβ amyloid plaque pathology in vivo in patients with Lewy body disorders. The burden of cortical Lewy bodies in case 3 was comparable to that

Figure 2 **Postmortem examination, microscopic (case 2)**



(A) Aβ (10D5) immunohistochemistry. Low-power micrograph shows extensive Aβ deposits in the frontal lobe; there is also cerebral amyloid angiopathy in some leptomeningeal vessels. (B) Hematoxylin and eosin. In the substantia nigra, there is neuronal loss, extracellular pigment, gliosis, and a Lewy body (arrow) in a surviving pigmented neuron. (C–F) α-synuclein (LB-509) immunohistochemistry. (C) Lewy bodies and a Lewy neurite in the substantia nigra are more readily seen by α-synuclein immunohistochemistry. (D) Lewy bodies are present in the parahippocampal gyrus. (E) Lewy bodies are present in subfield CA4 of the hippocampus. (F) Dystrophic neurites are present in the CA1/CA2 subfields of the hippocampus. (G) Phosphorylated tau (PHF-1) immunohistochemistry. Neurofibrillary tangles and neuropil threads are present in the parahippocampal gyrus. (A, D–F bar = 500 μm; B, C, G, bar = 100 μm.)

in the other 2 cases, yet cortical retention of PIB was not elevated in this individual. Only the 2 cases with high levels of cortical Aβ detected by immunohistochemistry had elevated cortical retention of PIB on in vivo imaging. Our methodology did not permit detailed quantitative correlations between regional PIB uptake and Aβ lesion burden on histopathology, as previously reported for a case of AD.[23] Nonetheless, all measured cortical regions with an elevated PIB binding potential (>0.2) in our study had severe (grade 3) Aβ plaque burden.

An unexpected finding in our study was that the 2 PIB-positive PDD cases had low probability AD by NIA-Reagan criteria. Evolving criteria for neuropathologic diagnosis of AD account for some of the conflicting results regarding the role of AD pathology in the pathogenesis of PDD.[1,33] Consortium to Establish a Registry for Alzheimer's Disease and NIA-Reagan criteria emphasize neuritic rather than diffuse Aβ plaques as the major correlate of dementia in AD. However, diffuse plaques may be the predominant pathology in the earliest, mild stages of AD, and may indicate preclinical AD in cognitively normal individuals.[20,34] The PIB-positive individuals in this study had more advanced dementia (CDR stage 2), a stage at which neuritic plaques are nearly universally present in patients with DAT.[35] Thus in the setting of PD, [^{11}C]-PIB PET may have insufficient specificity for antemortem diagnosis of comorbid AD due to the inability to distinguish between diffuse and neuritic Aβ plaques.

Since Lewy body pathology was advanced in all cases, regardless of Aβ burden, α-synucleinopathy was likely central to the pathogenesis of PDD in these individuals. However, since Aβ and α-synuclein pathologies may interact synergistically,[36] it is possible that the presence of diffuse Aβ plaque influences the evolution of dementia in individuals with PD, even in the absence of neurofibrillary tangle pathology indicative of comorbid AD. Diffuse Aβ plaques are typically abundant in cases with cortical Lewy bodies[37,38] and Lewy body counts are highly correlated with amyloid plaque counts in PD and PDD.[33,39] However, the timing of deposition of amyloid, Lewy bodies, and neurofibrillary tangles relative to clinical manifestations of dementia can only be inferred from postmortem studies. Serial imaging to measure the rate of amyloid deposition[40] in individuals with and without Lewy body disorders (subsequently confirmed by autopsy) can directly test whether α-synucleinopathy exacerbates amyloidosis and accelerates cognitive decline.[5] Likewise, prospective longitudinal follow-up of PIB-positive and PIB-negative individuals with PD will be valuable for ascertaining whether comorbid Aβ pathology influ-

Table 3 Regional molecular pathology[a]

	Case 1						Case 2						Case 3					
	Aβ			Tau		Syn	Aβ			Tau		Syn	Aβ			Tau		Syn
	DP	CP	CAA	NFT	NP	LB	DP	CP	CAA	NFT	NP	LB	DP	CP	CAA	NFT	NP	LB
Middle frontal gyrus (A)	3	2	1	1	0	3	3	1	0	1	0	2	1	0	0	0	0	2
Anterior cingulate gyrus	3	2	1	0	0	3	3	1	0	1	0	3	1	0	0	0	0	3
Prefrontal gyrus	3	1	1	0	0	3	3	1	0	1	0	2	0	0	0	0	0	3
Superior temporal gyrus (B)	3	1	1	1	0	3	3	1	0	1	1	3	0	0	0	0	0	2
Inferior parietal lobule	3	2	1	0	0	2	3	1	0	0	0	3	1	0	0	0	0	2
Occipital lobe (C)	1	1	2	0	0	0	2	1	1	0	0	0	0	0	0	0	0	1
Amygdala	3	1	0	1	0	4	3	1	0	1	0	3	0	0	0	0	0	3
Entorhinal cortex	3	1	1	2	0	3	3	1	0	2	0	3	0	0	0	1	0	3
Hippocampal CA1	1	0	0	1	1	2	0	0	0	1	0	1	0	0	0	1	0	2
Parahippocampal gyrus	3	1	1	3	1	3	2	1	0	2	1	3	0	0	0	1	0	3
Striatum (D)	3	0	0	0	0	1	3	1	0	1	0	1	1	0	0	0	0	1
Nucleus basalis of Meynert	3	1	1	1	0	3	3	0	0	1	0	3	0	0	0	1	0	3
Globus pallidus	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0
Thalamus	2	0	0	1	0	2	3	0	0	1	0	1	0	0	0	1	0	2
Substantia nigra	1	0	0	0	0	3	0	0	0	1	0	2	0	0	0	0	0	3
Locus coeruleus	1	0	0	1	0	1	1	0	0	0	0	3	0	0	0	0	0	3
Basis pontis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Medulla oblongata	0	0	0	0	0	3	0	0	0	1	0	3	0	0	0	0	0	3
Cerebellum	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1

CAA = cerebral amyloid angiopathy; CP = cored plaque; DP = diffuse plaque; LB = Lewy body; NFT = neurofibrillary tangle; NP = neuritic plaque; PIB = Pittsburgh Compound B; 0 = none; 1 = few/mild; 2 = moderate; 3 = severe; 4 (Lewy bodies only) = numerous/very severe.

[a]Letters in parentheses are provided for a subset of regions to facilitate cross-referencing to the corresponding PIB-PET imaging data presented in table 2.

ences the timing of onset, rate of progression, or spectrum of clinical manifestations in PDD. This information will be crucial for developing targeted therapies that can slow or prevent the onset of dementia in patients with PD.

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DISCLOSURE

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