Neuropathologic Substrates of Parkinson Disease Dementia

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Objective: A study was undertaken to examine the neuropathological substrates of cognitive dysfunction and dementia in Parkinson disease (PD).
Methods: One hundred forty patients with a clinical diagnosis of PD and either normal cognition or onset of dementia 2 or more years after motor symptoms (PDD) were studied. Patients with a clinical diagnosis of dementia with Lewy bodies were excluded. Autopsy records of genetic data and semiquantitative scores for the burden of neurofibrillary tangles, senile plaques, Lewy bodies (LBs), and Lewy neurites (LNs) and other pathologies were used to develop a multivariate logistic regression model to determine the independent association of these variables with dementia. Correlates of comorbid Alzheimer disease (AD) were also examined.
Results: Niney-two PD patients developed dementia, and 48 remained cognitively normal. Severity of cortical LB (CLB)/LN pathology was positively associated with dementia ($p < 0.001$), with an odds ratio (OR) of 4.06 (95% confidence interval [CI], 1.87–8.81), as was apolipoprotein E4 (APOE4) genotype ($p = 0.018$; OR, 4.19; 95% CI, 1.28–13.75). A total of 28.6% of all PD cases had sufficient pathology for comorbid AD, of whom 89.5% were demented. The neuropathological diagnosis of PDD+AD correlated with an older age of PD onset ($p = 0.001$; OR, 1.12; 95% CI, 1.04–1.21), higher CLB/LN burden ($p = 0.037$; OR, 2.48; 95% CI, 1.06–5.82), and cerebral amyloid angiopathy severity ($p = 0.032$; OR, 4.16; 95% CI, 1.13–15.30).
Interpretation: CLB/LN pathology is the most significant correlate of dementia in PD. Additionally, APOE4 genotype may independently influence the risk of dementia in PD. AD pathology was abundant in a subset of patients, and may modify the clinical phenotype. Thus, therapies that target α-synuclein, tau, or amyloid β could potentially improve cognitive performance in PD.

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Cognitive dysfunction and dementia are a significant nonmotor manifestation of Parkinson disease (PD), with up to 80% of patients developing dementia.[1] Cognitive dysfunction seriously compromises the ability to perform activities of daily living,[2] resulting in reduced independence, quality of life, and survival.[3,4] Clinically, cognitive deficits in PD with dementia (PDD) is similar, and often identical to, dementia with Lewy bodies (DLB)[5,6]; however, these typical features may be masked by an Alzheimer disease (AD)-like amnestic syndrome.[7]

PDD is a heterogeneous neuropathological entity. Multiple clinicopathological correlation studies have addressed this issue with conflicting results. Our group,[8] and others[9–12] have reported that cortical Lewy bodies (CLBs) or limbic[10,13] Lewy bodies (LBs) and Lewy neurites (LNs) are the best correlate of dementia in PD,

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indicating a caudal to rostral spread of LB/LN pathology from the brainstem to cerebral cortex, as proposed by Braak and colleagues.[14] However, others have found no correlations between cognitive function and the distribution of LBs in the brain.[15–17]

Comorbid AD pathology is also common in PDD,[11,18,19] and others have proposed that neurofibrillary tangle (NFT) and amyloid β (Aβ) senile plaque (SP) pathology[20,21] or a combination of these and CLBs/LNs form the neuropathological basis for PDD.[22] Furthermore, AD-specific neuroimaging[23] and cerebrospinal fluid[24] biomarkers are associated with cognitive impairment in PD. These overlapping features suggest a potential clinicopathological continuum between AD and PD.[25] Advances in immunohistochemical (IHC) methods and diagnostic criteria, together with variability in case selection, cognitive assessments, and small sample sizes may all contribute to these discrepancies.[9]

Here we present a large, well-characterized cohort of PD patients, followed longitudinally to autopsy at 2 major movement disorders centers in the United States. Detailed analysis of neuropathological and genetic data enabled us to determine the strongest correlates of dementia in PD, and examine the relationship between CLBs/LNs and AD pathology.

Patients and Methods

Patient Selection

One hundred forty patients with a clinical diagnosis of PD with and without dementia who had been treated at either the University of Pennsylvania's Parkinson's Disease and Movement Disorders Center or the Parkinson's Disease Research, Education, and Clinical Center at the Philadelphia VA Medical Center (Penn; n = 121; 40 PD, 81 PDD), or the Udall Parkinson's Disease Research Center at the University of Washington (UW; n = 19; 8 PD, 11 PDD) were selected for study. Forty-two patients (20 PD, 22 PDD) from Penn were described in a previous report.[8] Clinical diagnoses of PD and PDD were determined by the treating physician (J.E.D., J.B.L., H.I.H.) during life based on the United Kingdom Brain Bank[26] and the Diagnostic and Statistical Manual of the American Psychiatric Association (4th edition)[27] criteria. In most cases, patients were seen in clinic, or telephone contact was made with the patient or his/her family during the last 3 months of life. In addition, phone contact with the next of kin immediately after death provided additional information on cognitive status prior to death. Patients diagnosed with mild cognitive impairment were categorized in the nondemented group (n = 4). All patients had either normal cognition or dementia starting 2 or more years after the onset of PD motor symptoms. Patients with a clinical diagnosis of DLB or onset of dementia within 2 years of PD motor symptom onset were excluded. Genotyping for hereditary forms of PD was performed only in cases with significant family history. All cases were sporadic, with the exception of 1 *SCNA* triplication case.[28]

Neuropathological Assessment

Neuropathological examination was performed as previously described[8,29] with gross examination of fresh or fixed tissue. Informed consent was obtained in accordance with the rules of the respective institutional review boards at each university. Semiquantitative scores (0–3) for the major histological signatures of AD (NFTs, SPs) and PD (LBs/LNs) were determined for each case using IHC with established monoclonal antibodies for tau (PHF-1[30] or AT-8[31]) and alpha-synuclein (SYN303[32]). Mature SPs were evaluated by the amyloid-binding dye thioflavin-S (ThS) or tau IHC. Cerebral amyloid angiopathy (CAA) was evaluated in the midfrontal cortex using ThS. Scoring and postmortem diagnosis were performed by experienced neuropathologists (J.Q.T., T.J.M.) and later extracted from the Penn[33] and UW databases for use in the statistical analysis. Scoring of dystrophic LNs in the cornu ammonis (CA) region 2 and 3 of the hippocampus (CA2–3 LN)[34] was based on the highest density in these regions. The diagnosis of hippocampal sclerosis (HpScl) was established using the criteria of selective neuronal loss and gliosis in CA1 and subiculum as described.[35] The diagnosis of argyrophilic grain disease (AGD) was made by review of hippocampal sections with IHC for tau (n = 132) for the presence of dense tau-positive grains in the entorhinal cortex and mild to moderate involvement of the CA region, most consistent with a stage III[36] or higher of AGD pathology, together with pretangles in the dentate gyrus, and variable glial white matter pathology in the entorhinal cortex, as described.[36,37] Cerebrovascular disease (CVD) was defined based on the presence of vascular brain injury (VBI) using modified criteria outlined in the latest National Institute on Aging (NIA)-Alzheimer's Association (AA) guidelines.[38] Briefly, gross evidence of ischemic or hemorrhagic infarction or 2 or more microvascular lesions (MVLs) in 5 hematoxylin and eosin-stained sections (ie, thalamus, basal ganglia, and frontal, parietal, and temporal cortex) were considered positive for CVD. MVLs were enumerated at the time of neuropathological diagnosis and retrospectively confirmed for all cases. Evaluation of CA2–3 LN, HpScl, AGD, CVD, and missing database values were examined retrospectively at the time of this study. Staging of pathology was performed retrospectively using Braak[39] (NFTs), CERAD[40] (SPs), and McKeith[41] (LBs/LNs) criteria on regional semiquantitative data. Cases with an intermediate or high probability of AD[42] were classified as having comorbid AD. Seven cases with missing tissue/data precluded staging assessment in these cases. All retrospective analyses were performed blind to the clinical diagnosis.

Genetic Studies

DNA was extracted from peripheral blood following the manufacturer's protocols (Flexigene; Qiagen, Valencia, CA) or QuickGene DNA whole blood kit (Autogen, Holliston, MA). Genotyping was performed using real time allelic discrimination with Applied Biosystem (ABI, Foster City, CA) TaqMan probes. The

following single nucleotide polymorphisms were genotyped with the corresponding ABI assays: MAPT (rs1052553, C_7563736_10) and APOE (rs7412, C_904973_10 and rs429358, C_3084793_20). Genotyping was performed on an ABI 7500 real time instrument using standard conditions. Data were analyzed using ABI 7500 software v2.0.1.

Statistical Analysis

The global cortical score for burden of CLBs/LNs, SPs, and NFTs was determined by averaging semiquantitative scores in 5 cortical regions as described previously.[8] Briefly, the regions studied include the midfrontal, anterior cingulate, ventromedial–temporal (average of the amygdala, entorhinal cortex, and CA1–4), lateral–temporal, and parietal cortex. Available tissue in Wernicke's area or the superior/midtemporal cortex was used to evaluate the lateral–temporal lobe and postcentral or angular cortex was used for the parietal lobe. A cortical distribution score was calculated based on the number of these 5 cortical regions with a score >0. These whole number scores were designated as ordinal variables, as were raw scores from individual regions. Categorical variables included presence of HpScl, CVD, AGD, CAA, APOE4, and H1/H1 genotype. Continuous clinical variables included age of motor onset, age of dementia onset, age of death, disease duration, motor to dementia onset interval, and dementia onset to death interval. Demographic data were compared between groups using chi-square tests or Fisher exact tests for categorical variables, and independent t tests or Mann–Whitney U tests were used for continuous variables, as appropriate (Table 1).

A stepwise-selection model-building procedure was used to develop a logistic regression model to examine the association of these variables with the primary outcome of dementia in this cohort. Individual cortical region scores, AGD, CAA, and HpScl were excluded from the selection procedure due to limited data for these features in some groups, but were examined in the univariate analysis (Supplementary Table 1, Fig 1). A receiver operating characteristic (ROC) curve was generated to assess the diagnostic accuracy of the model.

Multiple logistic regressions were applied to the baseline model of dementia, controlling for age of death, gender, and APOE genotype to measure the independent effects of each cortical pathology type (Table 2). Categories with too few subjects were collapsed for analysis (i.e. Braak $\geq$ III-IV, CERAD $\geq$ A, NFT distribution score $\geq$ 2, SP distribution score $\geq$ 1). Finally, estimates of sensitivity and specificity for global cortical pathology scores were obtained at an optimal cutpoint, defined as the point that maximizes the sum of the specificity and sensitivity.

Stepwise-selection procedures incorporating all variables from the previous multivariate model were performed to determine correlates of the presence of comorbid AD and CLB/LN burden. All statistical tests were 2 sided, and significance set at the 0.05 level. Analyses were performed using SPSS 19.0 (SPSS, Chicago, IL) and R version 2.13.[43]

Results

Demographic Information

One hundred forty patients were included in the study (Table 1). Ninety-two developed dementia during the course of their illness, whereas 48 were judged by the clinician to be nondemented at the time of death. The 2 groups had similar age of motor onset and disease duration. The APOE4 allele was more prevalent in the PDD group ($p < 0.001$), whereas the proportion of H1/H1 haplotype carriers was similar between groups ($p = 0.223$).

Neuropathological Analysis

PDD patients had a significantly higher severity and wider distribution of cortical neuropathology for the 3 main lesion types studied (see Supplementary Table 1). In addition to semiquantitative measures, classification of disease burden differed significantly between the 2 groups, most notably with the PDD subgroup composed of exclusively limbic or neocortical LB/LN stage cases. Both Braak stages ($p = 0.009$) and CERAD scores ($p = 0.001$) were overall more advanced in the demented group; however, 9.1% of PD cases without dementia had significant pathology for a histologic diagnosis of comorbid AD. Conversely, 41.6% of the PDD group had no significant cortical SP pathology (CERAD 0), and 49.4% had minimal NFTs (Braak 0–II). Thus, comorbid AD was common, affecting a subgroup of PDD (38.2%). CAA was also more prevalent in PDD ($p = 0.003$). HpScl, CVD, AGD, CA2–3 LN and striatal NFTs, SP, and LB/LNs were not significantly different between groups (see Supplementary Table 1).

Regional analysis showed a significantly increased burden of SP and LB/LN pathology in the PDD group for all regions studied (see Fig 1). NFT density was significantly higher in the anterior cingulate gyrus and global cortical score only.

The associations between dementia and NFTS, SPs, and CLBs/LNs were assessed using logistic regression models. The likelihood ratio test was used in each model to determine whether the neuropathological variable contributed significantly to the fit of the model after adjusting for age at death, gender, and APOE status. All else being equal, increased CLB/LN global score, distribution score, and neocortical stage were associated with increased odds of dementia, as were advanced SP and NFT distribution and global cortical SP scores (see Table 2).

At the optimal cut points for the global cortical scores, CLBs/LNs have the highest sensitivity (74%; specificity, 67%) for dementia, whereas NFTs and SPs

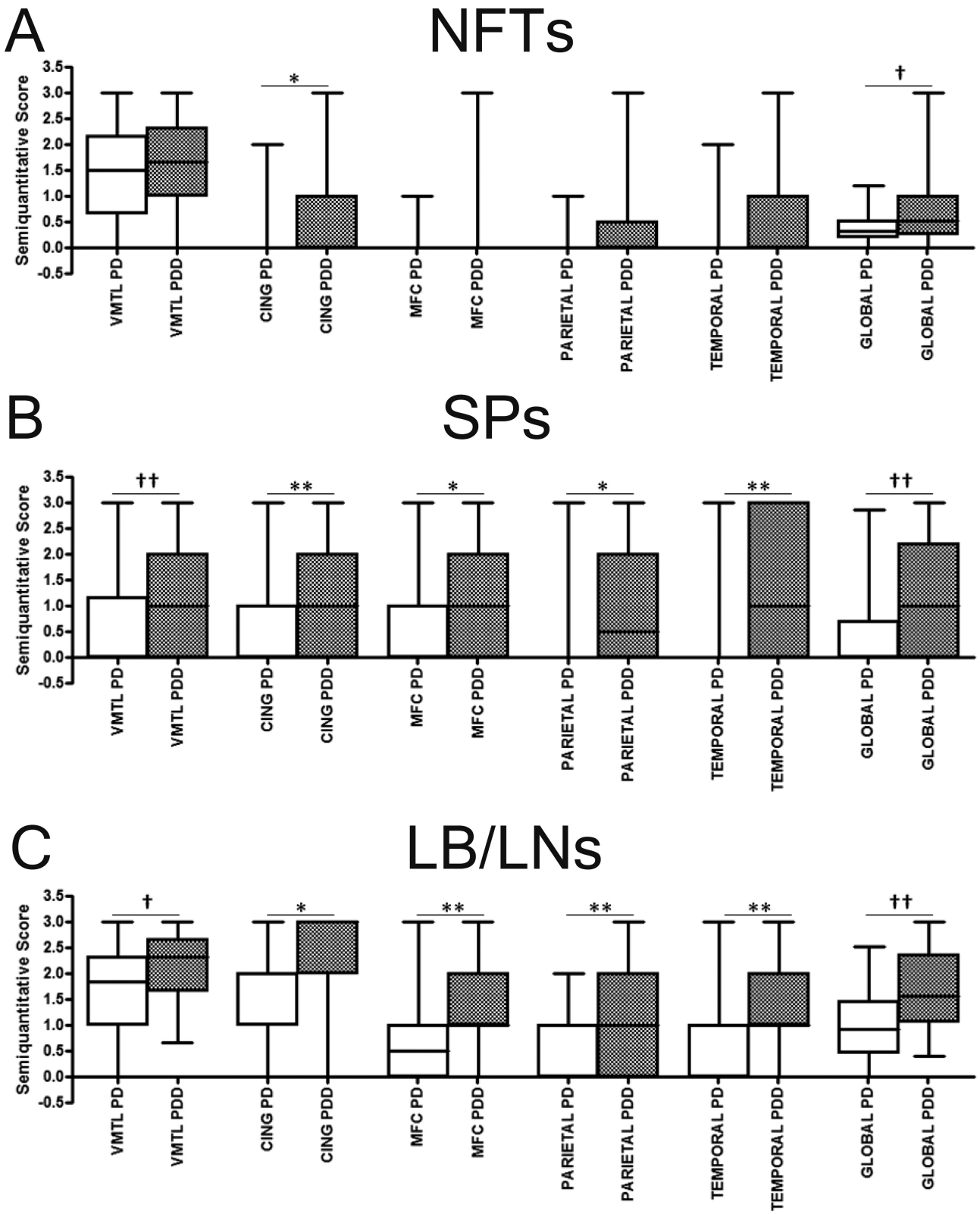


FIGURE 1: Box plots of cortical neuropathological burden by region for (A) tau neurofibrillary tangle (NFT) inclusions, (B) amyloid β senile plaques (SPs), and (C) α-synuclein–positive Lewy bodies (LBs)/Lewy neurites (LNs). *$p < 0.05$, **$p < 0.001$, chi-square test. †$p < 0.05$, ††$p < 0.001$, Mann–Whitney *U* test. CING = anterior cingulate gyrus; MFC = midfrontal cortex; PD= Parkinson disease; PDD = Parkinson disease with dementia; VMT = ventromedial temporal lobe.

TABLE 1: Demographic Information for Patient Groups

Characteristic	PD, n = 48	PDD, n = 92	*p*
Male, No. (%)	48 (70.8)	92 (78.3)	0.331[a]
Age of motor onset, median yr [IQR]	61.00 [48.75, 70.00][b]	63.50 [57.25, 71.75]	0.257[c]
Age of dementia onset, median yr [IQR]	NA	74.00 [69.25, 79.75]	NA
Age at death, median yr [IQR]	80.00 [72.00, 83.50]	79.00 [74.00, 82.00]	0.765[c]
Disease duration, median yr [IQR]	14.50 [9.75, 23.50][b]	13.00 [9.00, 19.00]	0.253[c]
Motor–dementia interval, median yr [IQR]	NA	8.00 [5.00, 14.00]	NA
Dementia–death interval, median yr [IQR]	NA	4.00 [2.00, 6.00]	NA
Brain weight, median g [IQR]	1,320.5 [1,177.8, 1,395.8]	1,300.0 [1,204.0, 1,423.0][d]	0.287[e]
APOE4 carriers, No. (%)	4/42 (9.5)	40/89 (44.9)	<0.001[a,f]
H1/H1 haplotype carriers, No. (%)	20/37 (54.1)	40/89 (44.9)	0.223[a]

[a]Chi-square test.
[b]Missing data for 2 cases.
[c]Mann–Whitney *U* test.
[d]Missing data for 1 case.
[e]Independent *t* test.
[f]Statistically significant.
IQR = interquartile range; NA = not applicable; PD = Parkinson disease; PDD = Parkinson disease with dementia.

have a higher specificity (75% and 86%, respectively; sensitivity, 55% for both; Fig 2).

Neuropathological Correlates of PDD

The stepwise-selection model-building procedure identified 2 significant correlates of dementia: CLB/LN score ($p < 0.001$; odds ratio [OR], 4. 06; 95% confidence interval [CI], 1.87–8.81) and APOE4 genotype carrier status ($p = 0.018$; OR, 4.19; 95% CI, 1.28–13.75; Table 3). We found no significant interaction between these variables, or between APOE4 genotype and measures of AD pathology or gender. The ROC curve obtained using this model (Fig 3) shows the high diagnostic performance of the model (area under the curve = 80.7%).

PDD Subgroup Analysis by Motor–Dementia Interval

Some studies have suggested an exponential rate of clinical progression in PD,[44] with older age of motor onset associated with a shorter motor–dementia interval (MDI) and higher burden of CLB/LN, SP, and NFT pathology.[22,45] Due to the large range in MDI in our cohort (2–30 years), we chose a similar stratification of the PDD group into short (MDI <10 years) and long MDI (MDI ≥10 years) groups to explore this phenomenon (Table 4). The short MDI cases were mostly male (88%, $p = 0.013$) and older at PD onset ($p < 0.001$), and had a shorter overall disease duration ($p < 0.001$). Furthermore, they had higher levels of cortical NFTs ($p = 0.003$) and CLBs/LNs ($p = 0.028$; Fig 4), with a higher percentage (47.8%) of comorbid AD ($p = 0.027$).

Relationship between AD and CLB Pathology in PDD

Using a stepwise-selection model, older age of PD onset ($p = 0.001$; OR, 1.12; 95% CI, 1.04–1.21), higher CLB/LN score ($p = 0.037$; OR, 2.48; 95% CI, 1.06–5.82), and increased severity of CAA ($p = 0.032$; OR, 4.16; 95% CI, 1.13–15.30) were found to be independently associated with PDD+AD (Table 5). Univariate analysis showed higher CLB/LN and CAA severity in the PDD+AD subgroup as well (see Fig 4, Supplementary Table 2).

To examine correlates of CLB/LN burden, a stepwise linear regression model showed increased global cortical NFT score ($p < 0.001$), presence of dementia ($p = 0.002$), CA2–3 LN score >1 ($p = 0.001$), and APOE4 carrier status ($p = 0.014$) to be significant (Table 6). There was also a significant interaction between APOE4 genotype and age of motor onset ($p = 0.048$); for APOE4 carriers, an earlier age of motor onset was associated with a higher CLB/LN burden. Age of motor onset was not significantly associated with CLB/LN burden in APOE4-negative patients ($p = 0.542$).

Discussion

Our detailed analysis of a large cohort of PD patients from 2 university-based PD movement disorder centers

TABLE 2: Correlation of Independent Neuropathologic Variables with Dementia in Parkinson Disease with Dementia

Measure[a]	OR (95% CI)[b]	*p*[c]
Staging		
Braak I–II	0.68 (0.12–3.94)	0.0151[d]
Braak ≥III–IV	2.58 (0.38–17.41)	
CERAD ≥A	1.99 (0.85–4.68)	0.1117
Neocortical LB/LN stage	5.80 (2.38–14.16)	0.0001[d]
Cortical severity		
Cortical NFT score	3.08 (0.95–9.99)	0.0316[d]
Cortical SP score	1.84 (1.14–2.97)	0.0082[d]
Cortical LB/LN score	4.15 (1.88–9.18)	0.0001[d]
Cortical distribution		
NFT distribution score ≥2	2.58 (1.03–6.44)	0.0384[d]
SP distribution score ≥1	2.43 (1.03–5.75)	0.0419[d]
LB/LN distribution score =3	2.33 (0.62–8.78)	0.0012[d]
LB/LN distribution score =4	5.50 (1.47–20.64)	
LB/LN distribution score =5	11.27 (2.84–44.7)	

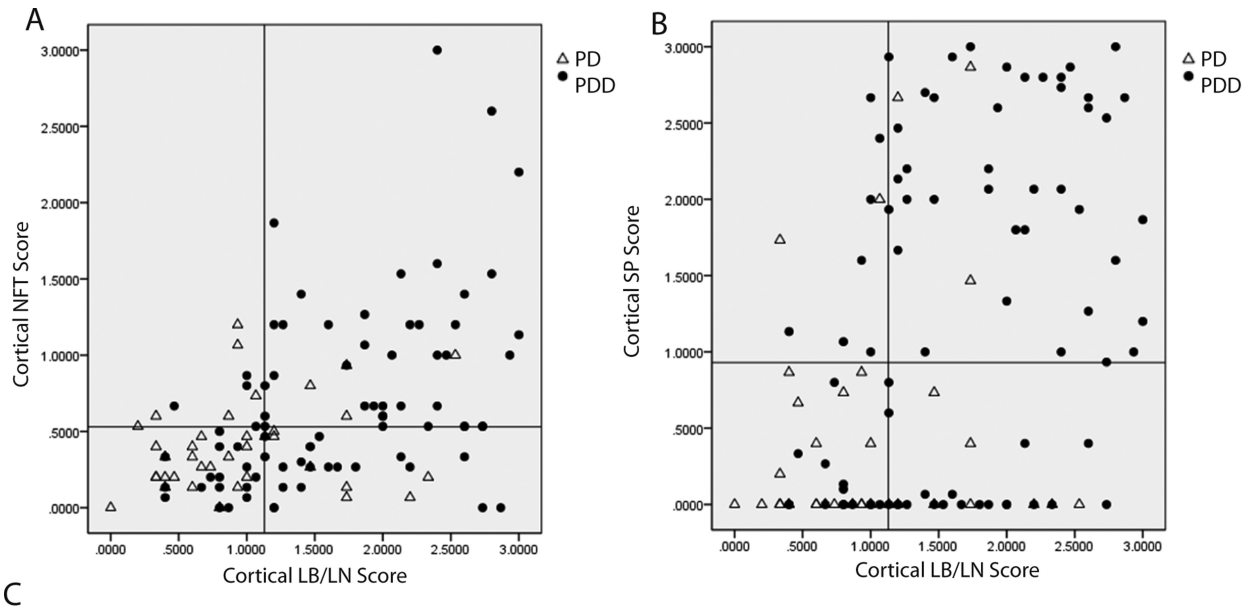
[a]Categories with <3 individuals were combined for analysis (ie, Braak stage, CERAD score, NFT distribution score, and SP distribution score).
[b]ORs and 95% CIs were generated from logistic regression models where the dependent (outcome) variable was presence of dementia. Age at death, gender, and APOE were included as covariates, and each neuropathological measure was analyzed in a separate model.
[c]Probability values were obtained from a likelihood ratio test comparing a model including age at death, gender, APOE, and the indicated neuropathological measure versus a model including age at death, gender, and APOE only.
[d]Statistically significant.
CERAD = Consortium to Establish a Registry for Alzheimer's Disease plaque score; OR = odds ratio; CI = confidence interval; LB = Lewy body; LN = Lewy neurite; NFT = neurofibrillary tangle; SP = senile plaque.

shows that the most robust correlate of dementia in PD is the severity of CLBs/LNs and APOE4 genotype. This combination of pathologies and genetic factors accounts for the majority of variability in our model. There was an independent contribution of NFTs and SPs for increased OR for dementia in PD, but these effects did not reach significance in the multivariate model; however, a thorough and comprehensive subanalysis of the PDD group that was designed to examine variables predictive of a comorbid AD diagnosis and demographics of PDD+AD patients suggests that plaque and tangle pathology may influence cognitive status and the course of disease progression in a subset of PDD patients.

These data confirm our previous report[8] of the importance of CLBs/LNs in the development of dementia in PD. Others have suggested that cognitive impairment in PD is due to a generalized process rather than involvement in specific regions.[9] We show here that CLB/LN density was greater in all cortical regions examined for PDD.

Subcortical basal ganglia SP[46] and LB/LN[32,46] pathology is often more robust in DLB than in PDD cases, and some studies also reported higher levels of SP[22,47] and LB/LN pathology[48] in PDD compared to PD. In this study, we examined a larger number of cases and found modest levels of SPs, NFTs, and LBs/LNs in the striatum for both demented and nondemented patients. Because we measured mature plaques only, the effect of other types of Aβ plaques or deposits in this study could be understated; however, other investigators have found a similar burden of diffuse plaques in PD and PDD groups.[22]

Although the optimal CLB/LN cutpoint was sensitive to detect the majority of PDD, it was less specific, mirroring previous data showing CLB/LN pathology in nondemented cases.[15,16] Thus, CLBs/LNs do correlate



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	Optimal Cut-point	Sensitivity% (95%CI)	Specificity% (95%CI)
Cortical NFT Score	0.53	55% (44-66%)	75% (62-88%)
Cortical SP Score	0.93	55% (45-66%)	86% (75-96%)
Cortical LB/LN Score	1.13	74% (65-84%)	67% (52-81%)

FIGURE 2: Diagnostic accuracy of neuropathology markers. Scatter plot of (A) cortical Lewy body (CLB)/Lewy neurite (LN) score and cortical tau neurofibrillary tangle (NFT) pathology score and (B) CLB/LN score and amyloid β senile plaque (SP) score for individual Parkinson disease (PD) cases stratified by presence of dementia. Lines represent optimal diagnostic cutpoints for sensitivity and specificity in given in C. CI = confidence interval; LB = Lewy body; PDD = PD with dementia.

significantly with cognitive impairment in the majority of PDD patients; however, differing thresholds resulting in the emergence of cognitive impairment during life may exist due to other factors, including APOE genotype as well as comorbid CVD and AD. All PDD cases in our series with minimal (<0.5) CLB/LN scores had comorbid CVD or significant subcortical pathology as a possible contributor to dementia (Supplementary Table 3).

The significant association of the APOE4 genotype with PDD in our cohort is intriguing and suggests an independent contribution to cognitive decline in PD, as there was no significant interaction between APOE4 carrier status and the global CLB/LN score or measures of AD neuropathology in our dementia model (see Table 3). Despite the lack of significance of this interaction, the APOE4 genotype was a significant correlate in

TABLE 3: Stepwise Selection Logistic Regression Model to Predict Parkinson Disease with Dementia

Variable	Estimate	SE	*z*	*p*	Odds Ratio	95% Confidence Interval
Intercept	−1.37	0.50	−2.73	0.0063	0.25	0.10–0.63
Global cortical LB/LN score	1.40	0.40	3.53	0.0004	4.06	1.87–8.81
APOE4 carrier	1.43	0.61	2.44	0.0182	4.19	1.28–13.75

Based on 116 observations.
LB = Lewy body; LN = Lewy neurite; SE = standard error.

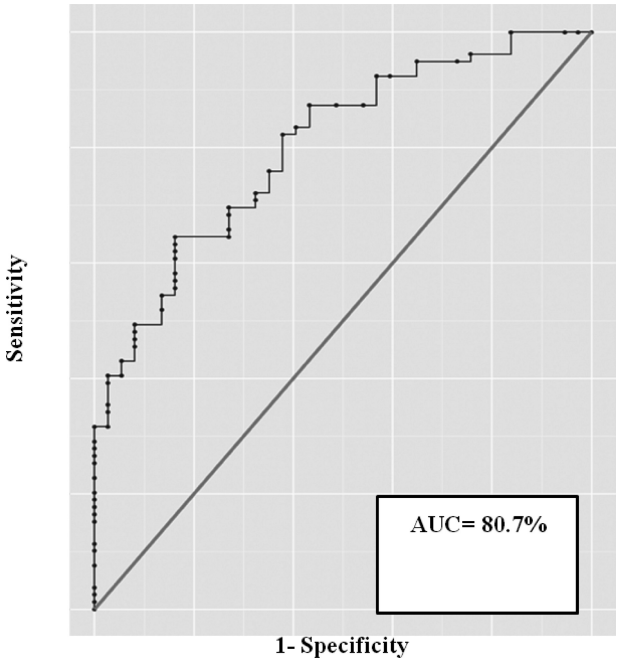

FIGURE 3: Accuracy of the multivariate model for dementia in Parkinson disease (PD). Receiver operating characteristic curve analysis of the combined variables cortical Lewy bodies/Lewy neurites and APOE4 genotype in predicting dementia in PD. AUC = area under the curve.

the multivariate regression model to predict a greater CLB/LN severity (see Table 6). Thus, the APOE4 genotype may contribute to cognitive decline in PD through both shared pathways associated with Lewy pathology and independent neurodegenerative pathways. Interestingly, in contrast to AD,[49] there was no interaction between APOE4 genotype and gender in our PD cohort, which may be due to the predominant number of male patients in our study. Others have also shown an effect of APOE genotype on PDD[50,51] and CLB/LN severity,[11] as well as a potential involvement of the APOE protein in cell[52] and animal models[53] of α-synuclein–mediated neurodegeneration, but further research is needed to elucidate the molecular mechanisms underlying these connections. Diagnostic accuracy was enhanced by incorporating both CLBs/LNs and APOE in the multivariate model for PDD (see Fig 3), implying that these factors influence cognitive impairment in the majority of PDD cases and that APOE genotype may be important to examine in clinical trials of PD involving cognitive outcomes.

Variability among previous studies may partly reflect the effects of CVD, because most clinicopathological studies of PDD did not evaluate CVD; however, 1 study found an association between advanced Braak NFT stage and CVD in PDD.[54] Thus, AD pathology may be additive in causing CVD in PDD. A reported inverse relationship between CVD and CLB/LN scores and direct correlation with CAA[55] suggest that AD-type pathology may accelerate CVD through associated CAA, independent of atherosclerosis and lipohyalinosis, and CVD may potentiate CLB/LN-associated cognitive impairment. Furthermore, APOE4 genotype confers a risk for vascular dementia both with and without comorbid AD.[56] We found that CAA was more common in PDD (see Supplementary Table 1), especially in those with comorbid AD; however, there was no unequivocal increased presence of CVD in the PDD and PDD+AD subgroups (see Supplementary Tables 1, 2), and CVD did not reach significance in our multivariate model of dementia. Our characterization of CVD was based on the neuropathological assessment in the recently revised NIA-AA AD guidelines,[38] and therefore our study was limited to measures of VBI. Further study and validation of the neuropathological correlates of VBI are needed; however, using the most recent criteria available, we do not show a significant influence of CVD on cognitive outcomes in PD.

Neither NFTs nor SPs were significant in our overall multivariate model of PDD. This notwithstanding, cortical NFT and SP severity scores were more specific for dementia than CLBs/LNs (see Fig 2), reflecting the high frequency of dementia in patients with sufficient pathology for a diagnosis of comorbid AD (89.5%). This finding suggests that PD patients, especially those with an older age of onset, may be at increased risk for developing AD. Hence, we speculate that this may reflect a double-hit model of cognitive impairment in PD, wherein AD and CLB/LN pathologies converge to cause distinct forms of cognitive impairment in PD/PDD. There were also independent associations of NFTs and SPs in the univariate analysis of dementia (see Table 2), indicating that these pathologies contribute to dementia in the subset of PDD+AD patients. The presence of a large proportion of PDD cases without significant AD pathology most likely explains why these measures may not be significant in the multivariate model. Furthermore, patients with comorbid AD had a shorter MDI (see Supplementary Table 2), suggesting an accelerated disease course. Thus, the presence of AD appears to be a relatively specific, although not exclusive,[19] finding in PDD that potentially modifies the clinical phenotype.[54] Others have shown a poorer prognosis for PDD cases with comorbid AD.[20]

Our finding that patients with a shorter MDI (<10 years) also have an older age of PD onset, shorter disease duration, and higher burden of comorbid AD pathology (see Table 4, Fig 4) agrees with previous reports,[20,22,44,45,57] although age of PD onset itself was

TABLE 4: Comparison of Long and Short MDI for PDD Patients

Characteristic	PDD, Short MDI, n = 50	PDD, Long MDI, n = 42	*p*
Male, No. (%)	44/50 (88.0)	28/42 (66.7)	0.013[a,b]
Age of motor onset, median yr [IQR]	69.50 [64.75, 75.25]	58.50 [50.00, 63.00]	<0.001[b,c]
Age of dementia onset, median yr [IQR]	74.00 [71.25, 80.00]	74.50 [68.75, 77.75]	0.540[c]
Age at death, median yr [IQR]	79.00 [73.00, 83.25]	78.00 [74.00, 81.25]	0.718[c]
Disease duration, median yr [IQR]	9.00 [8.00, 11.25]	19.50 [15.75, 23.00]	<0.001[b,c]
Motor–dementia interval, median yr [IQR]	5.00 [4.00, 8.00]	14.00 [12.00, 19.00]	NA
Dementia–death interval, median yr [IQR]	4.00 [2.00, 6.00]	3.50 [1.00, 6.00]	0.889[c]
Brain weight, median g [IQR]	1,308.00 [1,220.0, 1,486.0][d]	1,285.5 [1,185.25, 1,400.0]	0.125[e]
APOE4 carriers, No. (%)	23/48 (47.9)	17/41 (41.5)	0.542[a]
H1/H1 haplotype carriers, No. (%)	25/37 (67.6)	26/40 (65.0)	0.639[a]
Braak stage, No. (%)			0.010[a,b]
0	1/46 (2.2)	6/40 (15.0)	
I–II	15/46 (32.6)	20/40 (50.0)	
III–IV	15/46 (32.6)	8/40 (20.0)	
V–VI	15/46 (32.6)	6/40 (15.0)	
CERAD stage, No. (%)			0.121[a]
0	14/46 (30.4)	23/42 (54.8)	
A	3/46 (6.5)	2/42 (4.8)	
B	11/46 (23.9)	7/42 (16.7)	
C	18/46 (39.1)	10/42 (23.8)	
AD diagnosis, No. (%)	22/46 (47.8)	11/40 (27.5)	0.027[a,b]
LB/LN stage No. (%)			0.019[a,b]
Brainstem	0/48 (0.0)	0/39 (0.0)	
Limbic	4/48 (8.3)	11/39 (28.2)	
Neocortical	44/48 (91.7)	28/39 (74.4)	
Global cortical NFT			0.003[b,c]
No.	42	38	
Median [IQR]	0.67 [0.33, 1.2]	0.43 [0.13, 0.67]	
Global cortical SP			0.112[c]
No.	45	40	
Median [IQR]	1.6 [0.03, 2.50]	0.33 [0.00, 2.10]	
Global cortical LB/LN			0.028[b,c]
No.	44	38	
Median [IQR]	1.87 [1.22, 2.50]	1.20 [1.00, 2.13]	

[a]Chi-square test.
[b]Statistically significant.
[c]Mann–Whitney *U* test.
[d]Missing data from 1 case.
[e]Independent *t* test.
AD = Alzheimer disease; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; IQR = interquartile range; LB = Lewy body; LN = Lewy neurite; MDI = motor–dementia interval; NFT = neurofibrillary tangle; PDD = Parkinson disease with dementia; SP = senile plaque.

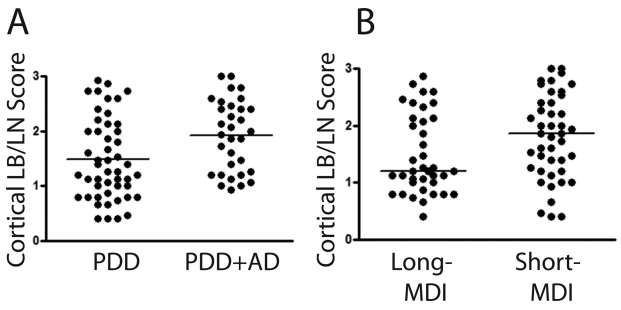

FIGURE 4: Scatter plot of cortical Lewy body (LB)/Lewy neurite (LN) score for individual Parkinson disease with dementia (PDD) subgroup cases (A) with (PDD+AD) and without (PDD) comorbid Alzheimer disease (AD; $p = 0.007$) and (B) short and long motor–dementia interval (MDI) PDD cases ($p = 0.028$). Bars represent median values.

not a significant correlate of dementia. Additionally, we show a similar dementia–death interval between PDD short and long MDI groups. This is in agreement with previous studies that have dissociated the effects of aging from the age of PD onset,[44,58] showing a stereotyped disease progression after the onset of dementia.

We further demonstrate a link between PD and AD by showing a correlation of NFT severity with increasing CLB/LN burden. Other investigators have also found correlations of SPs[9,11,22,59,60] and NFTs[9,22] with CLB/LN burden in PDD. In vivo animal studies,[61] in vitro cross-seeding experiments,[62–64] and significant comorbid tau pathology in hereditary PD patients with the A53T *SCNA* gene mutation[65] suggest there are synergistic interactions between tau and α-synuclein that may contribute to a clinicopathological spectrum between PD and AD.

In summary, our work here provides fresh insight into the complex pathogenesis of dementia in PD, and further emphasizes the importance of CLBs, aging, comorbid AD pathology, and genetic susceptibility as pathological substrates of cognitive impairment and dementia in PD. Further research will be necessary to clarify the relative contribution of each of these strands before effective treatment can emerge.

TABLE 5: Stepwise Selection Logistic Regression Model to Predict a Secondary Diagnosis of Comorbid Alzheimer Disease in Parkinson Disease with Dementia Patients

Variable	Estimate	SE	*z*	*p*	Odds Ratio	95% Confidence Interval
Intercept	−9.82	2.66	−3.70	0.0002	<0.01	<0.01–0.01
Age of motor onset	0.12	0.04	3.19	0.0014	1.12	1.04–1.21
Global cortical LB/LN score	0.91	0.44	2.08	0.0372	2.48	1.06–5.82
CAA score	1.43	0.66	2.15	0.0319	4.16	1.13–15.30

Based on 81 observations.
CAA = cerebral amyloid angiopathy; LB = Lewy body; LN = Lewy neurite; SE = standard error.

TABLE 6: Stepwise Selection Linear Regression Model to Predict Global Cortical LB/LN Score

Variable	Estimate	SE	*t*	*p*
Intercept	0.40	0.37	1.07	0.2885
Global cortical NFT score	0.75	0.13	5.73	<0.0001
Clinical dementia	0.39	0.12	3.16	0.0021
LN CA2–3 score ≥1	0.45	0.13	3.45	0.0008
APOE4 carrier	1.82	0.73	2.49	0.0144
Age at motor onset	−0.003	0.01	−0.61	0.5424
APOE4/age at motor onset interaction	−0.02	0.01	−2.01	0.0476

Based on 104 observations.
LB = Lewy body; LN = Lewy neurite; NFT = neurofibrillary tangle; SE = standard error.

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Potential Conflicts of Interest

Nothing to report.

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