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Clinical Correlations With Lewy Body Pathology in *LRRK2*-Related Parkinson Disease

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Abstract

IMPORTANCE—Mutations in leucine-rich repeat kinase 2 (*LRRK2*) are the most common cause of genetic Parkinson disease (PD) known to date. The clinical features of manifesting *LRRK2* mutation carriers are generally indistinguishable from those of patients with sporadic PD. However, some PD cases associated with *LRRK2* mutations lack Lewy bodies (LBs), a neuropathological hallmark of PD. We investigated whether the presence or absence of LBs correlates with different clinical features in *LRRK2*-related PD.

OBSERVATIONS—We describe genetic, clinical, and neuropathological findings of 37 cases of *LRRK2*-related PD including 33 published and 4 unpublished cases through October 2013. Among the different mutations, the *LRRK2* p.G2019S mutation was most frequently associated with LB pathology. Nonmotor features of cognitive impairment/dementia, anxiety, and orthostatic hypotension were correlated with the presence of LBs. In contrast, a primarily motor phenotype was associated with a lack of LBs.

CONCLUSIONS AND RELEVANCE—To our knowledge, this is the first report of clinicopathological correlations in a series of *LRRK2*-related PD cases. Findings from this selected group of patients with PD demonstrated that parkinsonian motor features can occur in the absence of LBs. However, LB pathology in *LRRK2*-related PD may be a marker for a broader parkinsonian symptom complex including cognitive impairment.

Mutations in leucine-rich repeat kinase2 (*LRRK2*)are the most frequent cause of genetic Parkinson disease (PD), accounting for at least 4% of autosomal dominant forms of familial PD and 1% of sporadic PD worldwide.[1] The *LRRK2* gene encodes a large multidomain protein that includes an enzymatically active central region surrounded by a series of putative protein-protein interaction domains.[2] Disease-causing mutations are concentrated within the central region of the protein, which contains an ROC GTPase domain, a COR sequence, and a serine/threonine kinase domain. Thus far, at least 8 mutations(p.N1437H,p.R1441C/G/H,p.Y1699C,p.G2019S,p.I2020T, and possibly p.I1371V) are considered to be pathogenic.p.G2019S is the most frequent mutation but penetrance of p.G2019S and other pathogenic *LRRK2* mutations is incomplete.[3-5]

The clinical presentation of manifesting *LRRK2* mutation carriers tends to be indistinguishable from that of sporadic PD, with mean age at onset of approximately 60 years and appreciable response to levodopa.[6] Conversely, the neuropathological features can be a typical for PD and heterogeneous even within kindreds.[7] In particular, autopsy studies have revealed that Lewy bodies (LBs), which are large intraneuronal protein aggregates consisting primarily of α-synuclein,[8] are absent in a significant subset of cases. This was a

surprising finding because LBs are neuro-pathological hallmarks of PD thought to be central to the neurodegenerative process and the clinical expression of PD and other synucleinopathies. Here we investigated the correlation of clinical features with LB pathology in *LRRK2*-related PD. This may provide insight into the relationship between α-synuclein pathology and specific features of the PD symptom complex.[9]

Methods

All published *LRRK2*-related autopsy cases up to October 2013 were identified by searching for English language articles in PubMed. The search terms *LRRK2*, *Lewy body/bodies*, *pathol ogy/pathological*, *neuropathology/neuropathological*, and/or *autopsy/autopsies* were used. Additional articles were found by searching the reference lists of identified articles and the authors' own files. Authors of published cases and directors of brain banks were contacted to identify unpublished cases. Clinical data were extracted from published articles. Additional data were obtained by requesting that investigators complete a clinical data form (eFigure in the Supplement) if the patient's clinic record was available. Neuropathological data were extracted from published articles and/or pathology reports when available. Cases were excluded if the associated *LRRK2* mutation was not one of the putative pathogenic mutations (previously mentioned), the patient did not have a clinical diagnosis of PD, or there was minimal or no available clinical and/or pathological information. Epi Info 7 from the Centers for Disease Control and Prevention was used for data analysis (www.cdc.gov/epiinfo/). Categorical variables were compared using the Fisher exact test. Continuous variables were compared using the *t* test. Logistic regression was performed to adjust for disease duration and age at death. Adjustment for Alzheimer disease–related pathology was made, where indicated, using Braak neurofibrillary tangle stage, which was estimated from the available data and dichotomized (≤stage III and ≥ stage IV). When necessary, a flattening constant of 1 was added to each cell to allow an odds ratio to be calculated. No imputation was made for missing data; patients missing values on an outcome were not included in the analysis for that outcome. Because this was an exploratory study, no adjustments were made for multiple comparisons. Separate analyses were also performed for p.G2019S-only cases. The study was approved by the ethics board of the University Health Network, Toronto, Ontario, Canada.

Results

Fifty-nine autopsy cases with *LRRK2* variants were identified: 54 published and 5 unpublished cases. Twenty-two cases were excluded from the analysis: 3 with nonpathogenic variants; 2 nonmanifesting *LRRK2* mutation carriers without a clinical diagnosis of PD; and 17 with insufficient clinical and/or pathological data (eTable 1 in the Supplement). No cases were excluded for neurological disease other than PD. Thirty-seven *LRRK2*-related PD cases were included: 33 published and 4 unpublished cases (17 with LBs and 20 without LBs) (eTable 2 in the Supplement). Neuronal loss within the substantia nigra was reported for all of these cases except for 2, in which these data were not provided. There were very limited data on neuronal loss within other brain regions. The demographic and genetic features of all included cases are summarized in **Table 1**. All cases with a p.I2020T mutation were of Japanese ethnicity. Cases with or without LBs were similar with respect to

sex, disease duration, and age at death. Cases with LBs were more likely to have a p.G2019S mutation. The demographic features of p.G2019S cases (11 with LBs and 6 without LBs) are summarized in **Table 2**.

Table 3 provides a summary of the frequency of clinical features in *LRRK2* cases with or without LBs. Tremor was the most common presenting symptom for *LRRK2* patients regardless of the presence of LBs (65% for both groups). Cardinal motor symptoms, atypical features, levodopa responsiveness, and motor complications (see eFigure in the Supplement for details) occurred with similar frequency in both groups for all *LRRK2* cases and for the subset of p.G2019S cases. Certain nonmotor features (documented on history and/or examination) were more frequent among *LRRK2* cases with LBs. After adjusting for disease duration and age at death, cognitive impairment/dementia, anxiety, and orthostatic hypotension were associated with the presence of LBs (**Table 4**). Cognitive impairment/dementia and anxiety were also associated with the presence of LBs within the subgroup of cases with the p.G2019S mutation. The association between cognitive impairment/dementia and the presence of LBs was maintained after adjustment for the degree of Alzheimer disease–related pathology (odds ratio, 8.14; 95% CI, 1.46-45.47; $P = .02$ for all *LRRK2* cases and odds ratio, 76.03; 95% CI, 1.07-5414.76; $P = .047$ for only p.G2019S cases).

Discussion

To our knowledge, this study is the first report of clinicopatho-logical correlations in a series of *LRRK2*-related PD cases. We found that a primarily motor phenotype was associated with an absence of LBs. Parkinsonism (ie, bradykinesia plus rigidity, tremor, and/or postural instability) occurring independently of LB pathology has also been observed in the context of mutations in *PARK2*, which encodes parkin, where most autopsy reports describe an absence of LBs.[10] Conversely, LBs have been detected in the brains of people without the motor features of PD, an entity termed *incidental LB disease*. Our findings are consistent with these observations that LBs are neither necessary nor sufficient for the clinical expression of parkinsonism. Yet, there is strong evidence in experimental mouse models of PD that accumulation of α-synuclein aggregates in the substantia nigra pars compacta is associated with the death of dopaminergic neurons that harbor these aggregates with concomitant loss of tyrosine hydroxylase and dopamine metabolites in the dorsal striatum.[11] There is similar evidence linking α-synuclein aggregates in hippocampus to hippocampal neuron loss and cognitive impairment.[12] It is proposed that the neuropathological correlate of parkinsonian motor features is neuronal loss in the ventrolateral tier of the substantia nigra pars compacta.[8] However, loss of nigral neurons is also not specific for a diagnosis of PD because it occurs in many other neurodegenerative disorders with prominent parkinsonism such as progressive supranuclear palsy and multiple system atrophy.

The expression of nonmotor features in this series of *LRRK2*-related PD cases was found to be related to the presence of LBs. In particular, cognitive impairment/dementia, anxiety, and orthostatic hypotension were more likely to occur at some point during the disease course in patients who were found to have LBs at autopsy. Many nonmotor features tend to occur with longer disease duration and/or older age[13] but we did not find that these potential confounders accounted for the differences observed between those with or without LBs.

Evidence for an association between Lewy pathology and nonmotor symptoms has been previously demonstrated for cognitive impairment in PD. In particular, several studies have demonstrated a strong correlation between dementia and severity of cortical Lewy pathology.[14-16]

Based on our findings, we hypothesize that *LRRK2*-related PD with LBs is associated with more extensive neuro-degeneration whereas neuronal loss may be more restricted (eg, to the substantia nigra pars compacta) in cases lacking LBs. This would be similar to parkin-related PD in which there is frequently an absence of LBs, restricted neurodegeneration, and a relative lack of nonmotor features.[10] In patients with sporadic PD, cortical Lewy pathology correlates with dementia but Alzheimer disease plaques and tangles also contribute to their cognitive impairment.[16,17] It is possible that aggregates of proteins other than α-synuclein are contributors to the clinical expression of *LRRK2*-related PD. Standardized neuropathological assessments of a series of *LRRK2* autopsy cases, including semiquantitative measures of neuronal loss and examination of various protein aggregates in brain stem, subcortical, and cortical structures, are needed to further interrogate correlations with specific motor and nonmotor symptoms in *LRRK2*-related PD.

Prior reports have highlighted the occurrence of atypical neuropathological findings at autopsy for some manifesting *LRRK2* mutation carriers including pathology resembling progressive supranuclear palsy, multiple system atrophy, or frontotemporal lobar degeneration with ubiquitin-positive inclusions, presence of TDP-43 inclusions, and/or lack of LB pathology (eTable 2). Our assessment was limited to clinical correlations with LBs because this was the only neuropatho-logical feature available for all cases. Additional details—such as the presence of α-synuclein immunoreactive inclusions in neuronal processes (eg, Lewy neurites, dotlike structures, and axonal spheroids), degree of neuronal loss, involvement of extranigral structures, immunostaining results for other protein inclusions, and the distribution of these features—were unavailable for many cases so analysis of these other features could not be carried out here. Furthermore, there is a lack of standard operating procedures for the neuropathological diagnosis of PD[8] and methodological differences (eg, areas sampled, immunostaining performed, and types of antibodies used) among the different centers may have produced variable results. Ongoing and future efforts to standardize autopsy collection, handling, and reporting for *LRRK2*-related PD cases will help to provide data for more detailed clinicopatho-logical correlations.

The *LRRK2* autopsy cases used in this study were identified primarily from published reports; therefore, there is the potential for ascertainment bias. Furthermore, the cases came from differing sources (eg, individual cases, large kindreds, and brain banks). The clinical data acquired in the study were based on retrospective reports by the patients, caregivers, and/or treating physician. The nature of this study precluded standardized clinical assessments, which is a significant limitation. An additional limitation includes the potential for false-positive findings due to multiple comparisons. Regardless, our observations raise the hypothesis that LB pathology may be the underlying basis for cognitive dysfunction in *LRRK2* disease while at the same time being a marker for a broader parkinsonian symptom

complex in *LRRK2*-related PD. This can be tested in future prospective cohort studies of patients with *LRRK2* mutations.

An important unresolved question is: why are LBs absent in a subset of patients with *LRRK2*-related PD? The large number of cases reported from various centers demonstrates that LB-negative *LRRK2*-related PD is not an anomalous finding. Genotype cannot account for this finding because the subset of patients without LBs is not represented by 1 specific *LRRK2* mutation. The possibility that *LRRK2*-related PD represents a distinct disease from sporadic PD and thus can present with non-LB pathology is unlikely based on the significant clinical similarities between PD associated with *LRRK2* mutations and sporadic PD,[6] evidence from genome-wide association studies demonstrating that *LRRK2* polymorphisms are genetic risk factors for sporadic PD,[18] and experimental findings that implicate the LRRK2 protein in molecular pathways underlying PD pathogenesis.[2] While our study did not explain why LBs are sometimes absent in *LRRK2*-related PD, it contributes to the accumulating evidence that LBs alone cannot explain the pathogenesis of PD but other forms of α-synuclein may also play important roles.[19] Indeed, small soluble aggregates of α-synuclein have been isolated from the cortex of a patient with G2019S *LRRK2* PD without LBs.[20] Our study also supports the ongoing effort to reevaluate the pathological criteria used to define PD, in particular, deemphasizing LBs as a core feature.[21]

Conclusions

Lewy body pathology is not present in all patients with *LRRK2*-related PD. The mutation p.G2019S is more frequently associated with LB pathology compared with other *LRRK2* mutations. The classic parkinsonian motor symptoms can occur without LBs, and a primarily motor phenotype appears to be associated with an absence of LBs. The expression of certain nonmotor features, particularly cognitive impairment, anxiety, and orthostatic hypotension, is related to the presence of LBs. Thus, LB pathology in *LRRK2*-related PD may be a marker for a broader parkinsonian symptom complex.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and Genetic Features of all *LRRK2* Cases With and Without LB Pathology

Feature	With LBs (n = 17)	Without LBs (n = 20)	*P* Value
Male, %(no./No.)	23.5 (4/17)	40.0 (8/20)	.32
Race/ethnicity			
Non-Asian, % (no./No.)	92.9 (13/14)	57.9 (11/19)	.05
White non-Jewish, No.	10	10	
Ashkenazi Jewish, No.	3	1	
Asian, % (no./No.)	7.1 (1/14)	42.1 (8/19)	
Age at onset, mean (SD), y	56.0 (11.2)	61.0 (10.2)[a]	.17
Disease duration, mean (SD), y	19.2 (9.0)	16.2 (6.7)	.27
Age at death, mean (SD), y	75.2 (9.3)	77.2 (8.4)	.49
LRRK2 mutation			
p.G2019S, % (no./No.)	64.7 (11/17)	30.0 (6/20)	.05
Other, % (no./No.)	35.3 (6/17)	70.0 (14/20)	
p.I2020T, No.	1	8	
p.R1441C, No.	2	2	
p.R1441G, No.	0	2	
p.Y1699C, No.	1	2	
p.N1437H, No.	1	0	
p.I1371V, No.	1	0	

Abbreviations: LB, Lewy body; *LRRK2*, leucine-rich repeat kinase 2.

[a]Seventeen of 20 cases.

Table 2

Demographic Features of *LRRK2* p.G2019S Cases With and Without LB Pathology

Feature	With LBs (n = 11)	Without LBs (n = 6)	*P* Value
Male,%(no./No.)	36.4 (4/11)	50.0 (3/6)	.64
Race/ethnicity			
Ashkenazi Jewish, % (no./No.)	37.5 (3/8)	20.0 (1/5)	>.99
White non-Jewish, % (no./No.)	62.5 (5/8)	80.0 (4/5)	
Asian, % (no./No.)	0 (0/8)	0 (0/5)	
Age at onset, mean (SD), y	57.0 (12.8)	68.0 (7.5)	.07
Disease duration, mean (SD), y	21.1 (9.7)	13.5 (4.2)	.09
Age at death, mean (SD), y	78.1 (6.6)	81.5 (4.1)	.27
Family history of PD, % (no./No.)[a]	50.0 (5/10)	60.0 (3/5)	>.99

Abbreviations: LB, Lewy body; *LRRK2*, leucine-rich repeat kinase 2.

[a] At least 1 first-, second-, and/or third-degree relative with PD.

Table 3

Frequency of Clinical Features With or Without LB Pathology[a]

Feature	All *LRRK2* Cases (N = 37)			*LRRK2* p.G2019S Cases (n = 17)		
	With LBs (n = 17)	Without LBs (n = 20)	*P* Value	With LBs (n = 11)	Without LBs (n=6)	*P* Value
Motor features, % (no./No.)						
Bradykinesia	100 (17/17)	100 (18/18)	>.99	100 (11/11)	100 (5/5)	>.99
Rigidity	100 (17/17)	100 (15/15)	>.99	100 (11/11)	100 (6/6)	>.99
Tremor	94 (16/17)	94 (16/17)	>.99	91 (10/11)	100 (6/6)	>.99
Postural instability	100 (16/16)	92 (12/13)	.45	100 (11/11)	80 (4/5)	.31
Atypical features	17 (2/12)[b,c]	33 (3/9)[d]	.61	11 (1/9)[c]	0 (0/3)	>.99
Nonmotor features, % (no./No.)						
Cognitive impairment/dementia	67 (10/15)	20 (4/20)	.01	82 (9/11)	17 (1/6)	.03
Depression	79 (11/14)	38 (3/8)	.08	89 (8/9)	67 (2/3)	.45
Anxiety	82 (9/11)	0 (0/7)	.002	100 (8/8)	0 (0/3)	.006
Orthostatic hypotension	50 (6/12)	0 (0/13)	.005	63 (5/8)	0 (0/3)	.18
Urinary symptoms	40 (4/10)	25 (3/12)	.65	57 (4/7)	0 (0/2)	.44
Constipation	78 (7/9)	38 (5/13)	.10	100 (6/6)	100 (2/2)	>.99
Levodopa treatment, % (no./No.)						
Positive response[e]	80 (8/10)[f]	86 (12/14)[g]	>.99	71 (5/7)	60 (3/5)[g]	>.99
Fluctuations	67 (10/15)	80 (12/15)	.68	64 (7/11)	67 (4/6)	>.99
Dyskinesia	73 (11/15)	62 (8/13)	.69	80 (8/10)	50 (3/6)	.30
Maximum levodopa dose, mean (SD), mg	798 (431)	836 (504)	.85	741 (395)	840 (391)	.67
No. of cases	10	11		8	5	

Abbreviations: LB, Lewy body; *LRRK2*, leucine-rich repeat kinase 2.

[a] The results for the features in bold are statistically significant.

[b] One patient had supranucleargaze palsy.

[c] One patient had upper motor neuron signs and myoclonus.

[d] One patient had upper motor neuron signs, 1 patient had supranucleargaze palsy and upper motor neuron signs, and 1 patient had amyotrophy.

[e] Percentage of patients with moderate to marked levodopa response.

[f] One patient did not have a trial of levodopa.

[g] One patient could not tolerate levodopa.

Table 4

Clinical Correlates of LB Pathology in *LRRK2*-Associated Parkinson Disease[a,b]

	All *LRRK2* Cases (N = 37)		*LRRK2* p.G2019S Cases (n = 17)	
Feature	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Motor features				
Bradykinesia	0.95 (0.05-17.97)	.97	2.49 (0.08-80.81)	.61
Rigidity	1.22 (0.06-26.80)	.90	1.94 (0.07-53.77)	.69
Tremor	1.03 (0.04-26.52)	.99	0.60 (0.04-9.19)	.71
Postural instability	2.22 (0.16-30.44)	.55	4.55 (0.23-89.65)	.32
Atypical features	0.54 (0.05-6.19)	.62	1.38 (0.08-25.39)	.83
Nonmotor features				
Cognitive impairment/dementia	**9.74 (1.80-52.60)**	**.008**	**85.64 (1.52-4817.27)**	**.03**
Depression	3.06 (0.36-26.07)	.31	3.33 (0.06-184.51)	.56
Anxiety	**17.87 (1.37-233.28)**	**.03**	**24.69 (1.14-536.51)**	**.04**
Orthostatic hypotension	**12.03 (1.17-123.93)**	**.04**	4.35 (0.31-61.10)	.28
Urinary symptoms	2.25 (0.29-17.46)	.44	6.82 (0.36-130.83)	.20
Constipation	14.49 (0.78-267.71)	.07	1.95 (0.06-68.51)	.71
Levodopa treatment				
Positive response	0.11 (0.01-2.42)	.16	0.10 (0-3.21)	.19
Fluctuations	0.10 (0.01-1.53)	.10	0.14 (0.01-3.31)	.22
Dyskinesia	0.31 (0.02-4.72)	.40	0.92 (0.05-16.14)	.95

Abbreviations: LB, Lewy body; LRRK2, leucine-rich repeat kinase 2; OR, odds ratio.

[a] Adjusted for disease duration and age at death.

[b] The results for the features in bold are statistically significant.