

Comparison of Risk Factor Profiles in Incidental Lewy Body Disease and Parkinson Disease

Roberta Frigerio, MD; Hiroshige Fujishiro, PhD, MD; Demetrius M. Maraganore, MD; Kevin J. Klos, MD; Anthony DelleDonne, PhD; Michael G. Heckman, MS; Julia E. Crook, PhD; Keith A. Josephs, MST, MD; Joseph E. Parisi, MD; Bradley F. Boeve, MD; Dennis W. Dickson, MD; J. Eric Ahlskog, PhD, MD

Objective: To explore whether associations of potential risk factors for incidental Lewy body disease (iLBD) are similar to those for Parkinson disease (PD).

Design: Brain autopsy study (1988-2004) of subjects without evidence of neurodegenerative disease or tremor who were evaluated by at least 1 physician within 1 year of death. Researchers analyzed incidental Lewy pathology blinded to clinical abstraction.

Setting: Olmsted County, Minnesota.

Subjects: Residents of Olmsted County and the immediate vicinity aged older than 60 years.

Main Outcome Measures: Whether risk factors previously associated with PD in Olmsted County are also associated with iLBD.

Results: Of 235 subjects, 34 had iLBD (14.5%). The overall risk factor profiles for iLBD and PD were fairly similar between the 2 sets of odds ratio (OR) estimates, with

11 of 16 ORs in the same direction. Prior Olmsted County studies documented 7 risk factors with statistically significant associations with PD; for physician occupation and caffeine intake, the ORs for iLBD were in the same direction and statistically significant, whereas for education, head injury, and number of children, they were in the same direction but not significant; they were in the opposite direction but not statistically significant for depression and anxiety. Incidental Lewy body disease was not associated with various end-of-life conditions or causes of death, though these patients were slightly older and more likely cachectic.

Conclusions: Based on this exploratory study, iLBD and PD appear to have similar risk factor profiles. Thus, at least some cases of iLBD could represent preclinical PD, arrested PD, or a partial syndrome due to a lesser burden of causative factors. Incidental Lewy body disease is not explained by nonspecific end-of-life brain insults.

Arch Neurol. 2009;66(9):1114-1119

Author Affiliations:

Departments of Neurology (Drs Frigerio, Maraganore, Josephs, Boeve, and Ahlskog) and Laboratory Medicine and Pathology (Dr Parisi), Mayo Clinic, Rochester, Minnesota; Department of Neuroscience and Neuropathology (Drs Fujishiro, DelleDonne, and Dickson), and Biostatistics Unit (Mr Heckman and Dr Crook), Mayo Clinic, Jacksonville, Florida; and the Movement Disorder Clinic of Oklahoma, Tulsa (Dr Klos).

LEWY BODIES AND LEWY NEURITES are histopathologic hallmarks of Parkinson disease (PD), clinically characterized by not only motor disorder, but also cognitive/behavioral, neuropsychiatric features, sleep disorders, and autonomic dysfunction. The lifetime risk of PD has been estimated at 1.6%.¹ However, this contrasts with the incidence of Lewy body–related pathology. Among neurologically normal people aged 60 years and older, 8% to 17% have Lewy bodies on postmortem examination.²⁻⁴ This has been termed incidental Lewy body disease (iLBD).

A major revision in our conceptualization of PD was heralded by the publication of Braak PD staging.^{5,6} In this scheme, PD does not start in the dopaminergic substantia nigra, but rather in the lower brain-

stem, olfactory bulb, and autonomic system^{7,8}; only later does it involve higher brain levels. Although there are exceptions to the Braak pattern,⁹⁻¹³ it is consistent with most cases. Incidental Lewy body disease is crucial to this scheme and has been assumed to represent the earliest, preclinical stages of PD.^{14,15} Presumably, patients with iLBD would have developed PD if they lived longer or if the PD pathogenic process had not been arrested.

There are, however, alternative explanations for iLBD. Rather than representing the earliest PD state, iLBD might simply reflect low-grade brain insults accumulating over a lifetime or during agonal pre-mortem states. It might also reflect nonspecific brain aging processes akin to neurofibrillary tangles that accumulate with age.¹⁶ The assumption that iLBD represents preclinical or arrested PD requires validation.

A number of risk factors have been associated with PD. Many of these have been assessed in the population of Olmsted County, Minnesota, the location of the Rochester site of the Mayo Clinic. These risk factors include estrogen/ovarian status (in women),^{17,18} smoking, caffeine and alcohol consumption,¹⁹ anxiety or depression,²⁰ diabetes mellitus, cancer, stroke,²¹ education, occupation,²² head injury,²³ and number of children.²⁴ If iLBD represents pre-clinical or arrested PD, the epidemiologic risk factor profile should be similar in these 2 conditions.

In this study, we explored whether PD and iLBD may indeed share epidemiologic risk factors. We used the Mayo Clinic Tissue Registry, which serves as a repository of brain autopsy specimens for patients from Olmsted County and the immediate vicinity; and we used the Mayo Clinic records linkage system, which compiles medical information for patients from Olmsted County and the immediate vicinity. Thus, we compared risk factors from identified iLBD cases with those previously measured in our Olmsted County PD population. We also assessed whether iLBD segregated with various chronic diseases and agonal conditions, which might suggest that it is caused by nonspecific brain insults. Although the number of iLBD cases in this neuropathologic series is similar to or exceeds that of most other neuropathologic series, the analyses presented herein are intended to be exploratory because of the study's relatively small sample size.

METHODS

STUDY SUBJECTS

We used the Tissue Registry of the Mayo Clinic Rochester Epidemiology Project to identify subjects from Olmsted County and the immediate vicinity who died between 1988 and 2004 and had available brain autopsy tissues plus adequate Mayo medical records documenting no clinical evidence of neurodegenerative conditions. Inclusion criteria were (1) age older than 60 years at death; and (2) medical record documentation of at least 1 medical evaluation during the last year of life. Exclusion criteria were medical record documentation of (1) parkinsonism, tremor, dementia, or other neurodegenerative disorders; and (2) large structural brain lesions that might have interfered with the postmortem assessment for Lewy body pathology (eg, massive hemorrhage or stroke and large brain tumors).

NEUROPATHOLOGIC METHODS

For each brain, the frontal and temporal cortex, cingulate gyrus, hippocampus, nucleus basalis of Meynert, midbrain, pons, medulla, and spinal cord were sectioned. The formalin-fixed and paraffin-embedded sections from cortical and subcortical regions were stained with hematoxylin-eosin, thioflavine S, and phospho-tau, and α -synuclein microscopy was performed.^{4,25-27} The histological evaluation included region-specific, semiquantitative assessments of atrophy, neuronal loss, astrogliosis, Lewy bodies, and Lewy neurites. All neuropathologic assessments were performed with researchers blinded to the medical records abstraction findings.

MEDICAL RECORDS ABSTRACTION

Medical records were obtained using the medical records linkage system of the Rochester Epidemiology Project. These were

abstracted, focusing on specific exposures that had been previously assessed in published case-control or cohort studies of PD in the Olmsted County population.¹⁷⁻²⁴ We restricted our analyses to risk factors that were defined similarly if not identically between these previous studies of PD and this study of iLBD. These factors (listed alphabetically) included alcohol, anxiety, caffeine, cancer, depression, diabetes mellitus, education, estrogen therapy, head injury, number of children, occupations, oophorectomy, smoking, and stroke.

In addition to cancer and diabetes, we assessed various systemic illnesses or agonal states that might nonspecifically be associated with incidental brain pathology. These included cachexia, chemotherapy, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, hypertension, peripheral vascular disease, sudden unexpected death, and other terminal diseases. The medical records abstraction was performed blind to the neuropathologic findings.

STATISTICAL ANALYSIS

Associations between patient characteristics and iLBD were investigated using logistic regression models adjusted for age and sex. Odds ratios (ORs) were estimated along with 95% confidence intervals (CIs). Number of children was investigated for association only in men, in keeping with published findings for PD; and oophorectomy and estrogen replacement therapy were considered only in women. $P \leq .05$ was considered statistically significant. No adjustments for multiple comparisons were made in these exploratory analyses. Odds ratios for iLBD were compared with previous estimated ORs in PD primarily via exploratory graphical summaries; no test of agreement was conducted owing to the lack of independence of ORs and the inability of any such test to adjust for this. However, as a numerical summary of the degree of agreement between estimated ORs for iLBD and PD, Lin's concordance correlation coefficient²⁸ was estimated. The concordance correlation coefficient ranges from -1 to 1, with a value of 1 indicating perfect agreement. Statistical analyses were performed using SPLUS, version 8.0.1 (Insightful Corporation, Seattle, Washington).

RESULTS

Of the 235 subjects included in this study, 130 were women (55.3%). Incidental Lewy body disease, defined by the presence of α -synuclein immunoreactive neuronal or neuritic lesions in 1 or more selected brain regions, was neuropathologically documented in 34 subjects (14.5%); the remaining 201 cases without Lewy pathology served as normal controls. Of the iLBD cases, 18 were women (52.9%), which mirrored the sex distribution among the 235 total subjects. The mean duration of Mayo medical records (duration from first Mayo visit to death) was 48 years in the subjects with iLBD (range, 5-74 years), compared with a mean of 41 years (range, 2 months to 78 years) in the control group ($P = .02$). All but 16 subjects had medical records dating back at least 5 years pre mortem. There were frequent physician contacts during the last 5 years of life, with a median 20 physician visits among the iLBD cases (25th percentile, 2 visits per 5 years; 75th percentile, 24 visits per 5 years); the control subjects had a median 21 physician visits during that time (25th percentile, 11 visits per 5 years; 75th percentile, 31 visits per 5 years).

Table 1 lists the exposures previously studied in published case-control or cohort studies of PD in Olmsted

Table 1. Risk Factors Associated With iLBD^a and PD^b

Variable ^c	No. (%)		Association With iLBD ^d		Association With PD ^e	
	iLBD Cases (n=34)	Controls (n=201)	Estimated OR (95% CI)	P Value	Estimated OR (95% CI)	P Value
Age at death, mean (SD), range, y ^f	82 (10), 75-90	78 (9), 72-84	1.70 (1.10-2.64)	.02	NA	NA
Male sex	16 (47)	89 (44)	1.43 (0.66-3.10)	.36	NA	NA
History of smoking	20 (59)	127 (63)	1.08 (0.46-2.50)	.87	0.69 (0.45-1.08)	NS
History of alcohol use	23 (70)	122 (64)	1.61 (0.68-3.80)	.28	1.04 (0.61-1.76)	NS
History of caffeine use ^g	16 (67)	128 (84)	0.36 (0.14-0.96)	.04	0.35 (0.16-0.78)	.01
≥9 Years of education	29 (88)	157 (80)	2.65 (0.84-8.33)	.1	2.0 (1.1-3.6)	SIGNIF
Estrogen therapy, women only	0	11 (10)	0.24 (0.01-4.23)	.36	0.60 (0.22-1.65)	NS
History of head injury	1 (3)	5 (2)	1.44 (0.16-13.19)	.75	4.3 (1.2-15.2)	.02
Occupation as a physician	4 (12)	4 (2)	6.84 (1.46-32.06)	.02	3.7 (1.0-13.1)	.05
Occupation as a teacher	5 (15)	20 (10)	1.27 (0.42-3.89)	.67	1.1 (0.5-2.1)	.9
Occupation as a farmer	5 (15)	26 (13)	0.88 (0.29-2.62)	.81	1.1 (0.6-1.9)	.8
≥1 Children, men only	14 (88)	74 (83)	1.61 (0.32-8.02)	.56	2.65 (1.15-6.10)	.02
History of anxiety	3 (9)	41 (20)	0.40 (0.11-1.39)	.15	2.2 (1.4-3.4)	<.001
History of depression	8 (24)	59 (30)	0.72 (0.30-1.70)	.45	1.9 (1.1-3.2)	.02
Cancer	18 (53)	104 (52)	1.01 (0.48-2.11)	.98	1.4 (0.9-2.0)	NS
Stroke	11 (32)	40 (20)	1.73 (0.77-3.90)	.19	1.6 (0.8-3.2)	NS
Diabetes	5 (15)	45 (22)	0.74 (0.26-2.08)	.57	0.7 (0.4-1.4)	NS
Oophorectomy, women only	0	6 (5)	0.43 (0.02-8.05)	.70	1.80 (0.93-3.45)	.08

Abbreviations: CI, confidence interval; iLBD, incidental Lewy body disease; NA, not available; NS, not significant; OR, odds ratio; PD, Parkinson disease; SIGNIF, significant.

^aCurrent Olmsted County, Minnesota, study.

^bPrevious Olmsted County, Minnesota, study.

^cInformation was unavailable for the following variables: history of alcohol use (n=10), history of caffeine use (n=61), years of education (n=5), and oophorectomy in women (n=2).

^dOdds ratios and *P* values resulted from logistic regression models adjusted for age and sex for all variables except estrogen therapy and oophorectomy, in which, owing to the lack of iLBD cases with those characteristics, ORs resulted from adding 0.5 to each cell count and *P* values resulted from Fisher exact test.

^eOdds ratios and *P* values resulted from conditional logistic regression models adjusted for various covariates in age- and sex-matched case-control or cohort studies from the same patient population as the iLBD case-control study. Specific *P* values were not available in some published articles.

^fOdds ratios correspond to a 10-year increase.

^gCaffeine use was focused on coffee use in the PD case-control study, whereas all caffeine use was considered in the iLBD case-control study.

Table 2. Power to Detect Odds Ratios With 34 Cases of Incidental Lewy Body Disease and 201 Controls

Characteristic Frequency, %	Power to Detect Given Odds Ratio, %						
	1.2	1.5	2.0	2.5	3.0	3.5	4.0
10	3	8	21	37	51	62	71
20	4	12	33	54	70	82	89
30	4	14	38	61	78	88	93
50	4	14	36	59	75	86	92

County.¹⁷⁻²⁴ The largest of the case-control PD studies had 197 PD cases and 197 matched controls. The cohort study involving oophorectomy had a substantially larger number of patients (2327 with oophorectomy and 2280 without).¹⁷⁻²⁴

In the current study, there was evidence of an increased risk of iLBD in subjects who were physicians (OR, 6.84; 95% CI, 1.46-32.06; *P* = .02), which was also observed in the PD study (OR, 3.7; 95% CI, 1.0-13.1). There was a reduced risk of iLBD in subjects who ever drank caffeinated beverages (OR, 0.36; 95% CI, 0.14-0.96; *P* = .04), which again was observed in the PD study (OR, 0.35; 95% CI, 0.15-0.78). There was a nonstatistically significant association of iLBD with higher education (≥9 years; OR, 2.65; 95% CI, 0.84-8.33, *P* = .1), which was similar in magnitude and statistically significant in the PD study (OR, 2.0; 95% CI, 1.1-3.6). Of the remaining 4 risk factors with

statistically significant associations with PD, ORs for iLBD were in the same direction but not statistically significant for history of head injury (iLBD, 1.44; PD, 4.3) or number of children in men (iLBD, 1.61; PD, 2.65); they were in the opposite direction but not statistically significant for depression (iLBD, 0.72; PD, 1.9) or anxiety (iLBD, 0.40; PD, 2.2). **Table 2** summarizes ORs estimated for each risk factor in iLBD and PD according to magnitude and statistical significance of each OR. Age was also associated with an increased risk of iLBD (OR, 1.70 [10-year increase]; 95% CI, 1.10-2.64; *P* = .02); we did not have an OR for age and PD in the same population.

Figure, A, is a graphical representation comparing risk factors in iLBD and PD. **Figure, B**, offers an alternate comparison of risk factors in iLBD and PD. When comparing ORs of risk factors for iLBD and PD, it is important to take into account the degree of precision of ORs, particularly

for several ORs associated with iLBD, for which the 95% CIs were particularly wide (estrogen use in women, oophorectomy in women, history of head injury, number of children in men, and occupation as a physician). For 11 of 16 risk factors, iLBD and PD had ORs in the same direction. Only anxiety, depression, farming occupation, oophorectomy, and smoking had ORs with different directions. Of those, the ORs for farming (iLBD, 0.88; PD, 1.1) were both relatively close to 1. Lin's concordance correlation coefficient²⁸ measuring the level of agreement between all iLBD and PD ORs was equal to 0.52, which in the context of this study can reasonably be considered to represent moderate to good agreement.

We had only limited statistical power to detect associations of the risk factors with iLBD. A large reason for this was that only 14.5% of neuropathologic examinations yielded iLBD cases. The previously published Olmsted County epidemiologic studies of patients with PD included larger samples. Table 2 provides the statistical power for a range of frequencies and ORs in 34 cases and 201 controls. Given this limitation and also the lack of power in the moderately sized PD case-control studies, we examined the overall pattern of the associations in addition to statistical significance of those associations.

We also compared the iLBD group (n=34) with the normal control subjects (n=201) with respect to systemic illnesses and nonspecific end-of-life medical states that might suggest a nonspecific etiology (**Table 3**). After adjusting for age and sex, there was a significant association of iLBD with only 1 of these 11 factors: chronic cachexia (OR, 3.25; 95% CI, 1.10-9.59; $P=.03$).

COMMENT

The epidemiological risk factor profile for iLBD in our autopsy sample was fairly similar to the one for PD that was previously reported in a similar Olmsted County population. The direction of the ORs was the same for 11 of the 16 factors we assessed. Of the 7 risk factors with statistically significant associations with PD, 5 had ORs in the same direction for iLBD, with 2 statistically significant associations and 1 borderline significant association. Although a larger sample with more patients with iLBD is necessary to make strong conclusions, these findings are consistent with the hypothesis that iLBD is indeed related to PD. This hypothesis is supported by 3 other clinical observations previously reported in iLBD, which documented rapid eye movement sleep behavior disorder,^{15,29} reduced bowel movement frequency,³⁰ as well as olfactory dysfunction³¹ similar to PD.

We also assessed a battery of medical conditions that might result in chronic low-grade brain insults (nonspecific to PD). Incidental Lewy body disease was only associated with chronic cachexia, which could be an effect of the disease rather than its cause (cause-effect inversion). Although the subjects with iLBD were slightly older (by a mean of 4 years), this small difference seems unlikely to account for the iLBD status. These findings argue against the hypothesis that iLBD is a nonspecific finding unrelated to PD.

Nonclinical evidence also suggests that iLBD is closely linked to PD. Two recent studies independently docu-

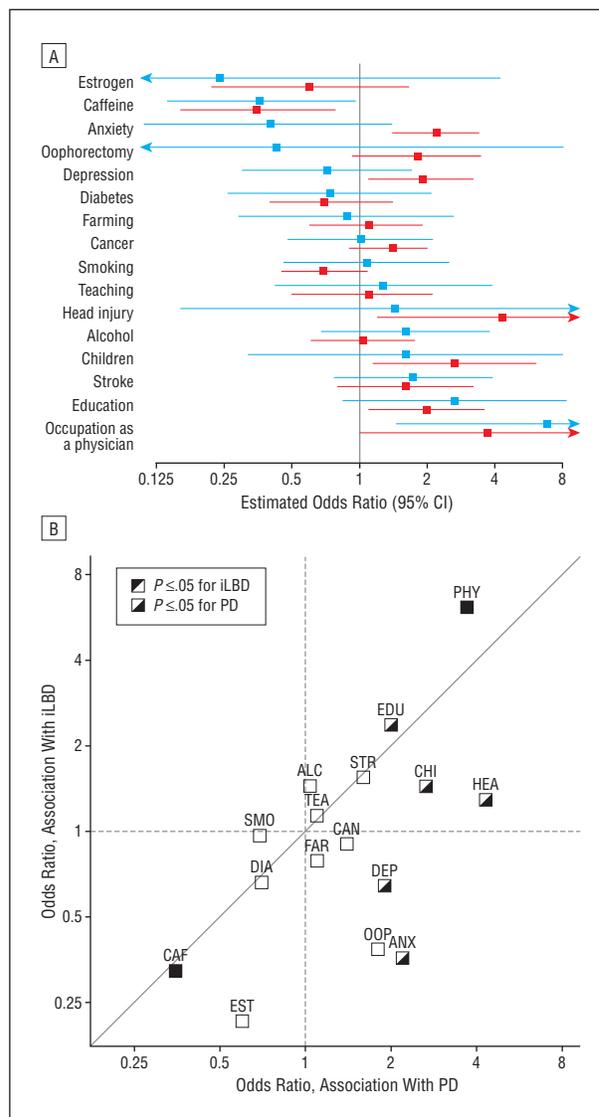


Figure. Association of risk factors with incidental Lewy body disease (iLBD) and Parkinson disease (PD) in Olmsted County, Minnesota. A, Pooled data analysis (blue represents iLBD; red, PD). B, Scatterplot of odds ratios for risk factors observed for PD vs iLBD. ALC indicates alcohol; ANX, anxiety; CAF, caffeine; CAN, cancer; CHI, children; CI, confidence interval; DIA, diabetes; DEP, depression; EDU, education; EST, estrogen; FAR, farming; HEA, head injury; OOP, oophorectomy; PHY, physician as occupation; SMO, smoking; STR, stroke; and TEA, teaching.

mented reduced striatal dopaminergic terminal markers among iLBD cases, with values intermediately between those of normal control subjects and PD cases.^{26,32} Moreover, the topography of Lewy pathology in iLBD mirrors PD, affecting not only the same brain regions,^{5,6} but also the autonomic nervous system.^{3,4,7,8,27,33,34} Thus, unlike tangles and tau pathology, which may have a more ubiquitous distribution in advanced age,¹⁶ iLBD follows the topographic pattern of PD.

One curious finding in this study was the association of physician occupation with iLBD (OR, 6.84; 95% CI, 1.46-32.06; $P=.02$). We previously reported a similar association of being a physician with PD, but attributed that finding to surveillance bias (ie, physicians would be more likely to recognize parkinsonism in themselves). This parallel

Table 3. Association of Nonspecific Systemic Illnesses and End-of-Life Medical States With iLBD

Variable	No. (%)		Estimated OR (95% CI) ^a	P Value ^a
	iLBD Cases (n=34)	Controls (n=201)		
Diabetes	5 (15)	45 (22)	0.74 (0.26-2.08)	.57
Insulin-dependent diabetes	2 (6)	18 (9)	0.90 (0.19-4.26)	.90
High blood pressure	20 (61)	142 (71)	0.67 (0.31-1.45)	.31
Terminal disease	12 (35)	71 (35)	1.03 (0.48-2.23)	.94
COPD	7 (21)	61 (30)	0.64 (0.26-1.56)	.32
Cancer	18 (53)	104 (52)	1.01 (0.48-2.11)	.98
Metastatic cancer	3 (9)	26 (13)	0.73 (0.20-2.60)	.63
Chemotherapy	3 (9)	27 (13)	0.87 (0.24-3.19)	.84
CAD	14 (41)	108 (54)	0.61 (0.29-1.29)	.20
PVD	6 (18)	30 (15)	1.31 (0.49-3.51)	.59
Sudden unexpected death	5 (15)	25 (12)	1.40 (0.43-3.64)	.68
Cachexia	6 (18)	14 (7)	3.25 (1.10-9.59)	.03

Abbreviations: CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; iLBD, incidental Lewy body disease; OR, odds ratio; PVD, peripheral vascular disease.

^aFrom logistic regression models adjusted for age and sex.

finding in iLBD suggests that the association of occupation as a physician with PD is not due to surveillance bias.

As in PD, caffeine consumption was associated with a reduced risk of iLBD. Although caffeine might protect against Lewy pathology and PD, it is also possible that caffeine aversion (as well as the choice of physician as an occupation) is an early behavioral manifestation of Lewy pathology (cause-effect inversion). Premorbid personality differences have been reported in PD.³⁵⁻³⁷

This study is not without its limitations. Chief among these is the relatively small number of iLBD cases, which results in low power to detect statistically significant associations and correspondingly wide CIs for estimated ORs, indicating a lack of precision in these estimates. A sample with more patients with iLBD is needed to better evaluate associations with iLBD. With that said, though this is a small number of cases compared with epidemiologic studies of PD cases, the number of iLBD cases in this neuropathologic series is similar to or exceeds that of most other neuropathologic series. Approximately 7 to 10 brains must be microscopically examined across multiple brain regions to detect 1 case of iLBD.

Because our iLBD cases were not prospectively examined by a neurologist during the patient's life, it is possible that PD may have been overlooked. However, the incidence of iLBD in our series (14.5%) is nearly 10 times greater than the lifetime risk (1.6%) for PD in the Olmsted County population.¹ This suggests that most of the iLBD cases included in our study were not simply undetected cases of PD.

It is unlikely that the risk factors that we observed for either iLBD or PD in the Olmsted County population are due to measurement biases. The medical records abstraction was blinded to the neuropathology and conversely, the neuropathologic analyses were blinded to the medical records abstraction. Since our iLBD cases were clinically undetected, there were obviously no recall biases. The medical records provided a rich source of data, with mean durations of Mayo records spanning 4 decades in both the iLBD and control groups. All subjects had been

evaluated by a physician at least once in the last year of life and very frequently during the last half decade (median, 20-21 physician visits during the last 5 years of life).

Finally, it should be noted that among the 34 iLBD cases, 13 were a distinctly poor fit with the Braak ascending scheme; 12 cases had diffuse Lewy pathology consistent with Braak stages 5 to 6, and 1 had Lewy pathology in only the nucleus basalis. Whether these outliers represent a unique iLBD subset is open to speculation. We reanalyzed the data confined to the 21 remaining cases. In this reanalysis, the ORs for these iLBD cases were in the same direction as PD for 12 of the 16 variables (compared with 11 of 16 for the entire iLBD cohort of 34 cases). In addition, the Lin correlation coefficient increased from 0.52 to 0.58, consistent with a slightly greater association of these 21 iLBD cases with PD. With this smaller sample, however, none of the PD-related variables reached statistical significance.

Overall, these findings are reasonably consistent with the hypothesis that at least some iLBD cases are on a neurodegenerative disease continuum with PD, ie, they represent an early stage in the PD process. However, if this hypothesis is correct, it remains unknown if such iLBD cases might represent individuals with preclinical PD who died before clinical manifestation or arrested PD, with some unknown factor terminating the progression to PD. Alternatively, if PD is due to the additive effects of multiple factors, iLBD might reflect an incomplete syndrome, with subthreshold involvement of the same factors. Further study of iLBD cohorts may provide insights regarding factors that modify the progression of Lewy pathology and hence may suggest primary prevention strategies.

Accepted for Publication: April 16, 2009.

Correspondence: J. Eric Ahlskog, PhD, MD, Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN 55902 (eahlskog@mayo.edu).

Author Contributions: Dr Ahlskog had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design: Frigerio, Maraganore, DelleDonne, Dickson, and Ahlskog. **Acquisition of data:** Frigerio, Fujishiro, Klos, Parisi, Dickson, and Ahlskog. **Analysis and interpretation of data:** Frigerio, Fujishiro, Maraganore, Heckman, Crook, Josephs, Boeve, Dickson, and Ahlskog. **Drafting of the manuscript:** Frigerio, Maraganore, Dickson, and Ahlskog. **Critical revision of the manuscript for important intellectual content:** Fujishiro, Klos, DelleDonne, Heckman, Crook, Josephs, Parisi, Boeve, and Ahlskog. **Statistical analysis:** Heckman and Crook. **Obtained funding:** Dickson. **Administrative, technical, and material support:** Klos. **Study supervision:** DelleDonne and Ahlskog.

Financial Disclosure: Dr Maraganore reports submitting a provisional application for patent under law 37 CFR § 1.53 entitled "Predicting Parkinson's Disease." No monies have been awarded to date. Dr Maraganore also reports submitting a provisional application for a patent entitled "Method of Treating Neurodegenerative Disease" that has been licensed to Alnylam Pharmaceuticals Inc. Less than \$10 000 has been awarded to date; Dr Boeve reports having received grant support from Myriad Pharmaceuticals and honorarium from GE Healthcare.

Funding/Support: This work was supported by grant P50 NS40256 from the Morris K. Udall Parkinson's Disease Research Center of Excellence, grant 2R01 ES10751 from the National Institutes of Health, grant P50 AG16754 from the Mayo Alzheimer's Disease Research Center, and grant U01 AG06786 from the Mayo Alzheimer's Disease Patient Registry.

Additional Contributions: Mike Oelkers and Connie McDonough helped with the Tissue Registry, and Monica Casey-Castanedes, Virginia Phillips, and Linda Rouseau provided histological technical support.

REFERENCES

- Elbaz A, Bower JH, Maraganore DM, et al. Risk tables for parkinsonism and Parkinson's disease. *J Clin Epidemiol*. 2002;55(1):25-31.
- Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1988;51(6):745-752.
- Bloch A, Probst A, Bissig H, Adams H, Tolnay M. Alpha-synuclein pathology of the spinal and peripheral autonomic nervous system in neurologically unimpaired elderly subjects. *Neuropathol Appl Neurobiol*. 2006;32(3):284-295.
- Klos KJ, Ahlskog JE, Josephs KA, et al. Alpha-synuclein pathology in the spinal cords of neurologically asymptomatic aged individuals. *Neurology*. 2006;66(7):1100-1102.
- Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging*. 2003;24(2):197-211.
- Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res*. 2004;318(1):121-134.
- Braak H, de Vos RA, Bohl J, Del Tredici K. Gastric alpha-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology. *Neurosci Lett*. 2006;396(1):67-72.
- Braak H, Sastre M, Bohl JR, de Vos RA, Del Tredici K. Parkinson's disease: lesions in dorsal horn layer I, involvement of parasympathetic and sympathetic pre- and postganglionic neurons. *Acta Neuropathol*. 2007;113(4):421-429.
- Parkkinen L, Kauppinen T, Pirttila T, Autere JM, Alafuzoff I. Alpha-synuclein pathology does not predict extrapyramidal symptoms or dementia. *Ann Neurol*. 2005;57(1):82-91.
- Halliday G, Hely M, Reid W, Morris J. The progression of pathology in longitudinally followed patients with Parkinson's disease. *Acta Neuropathol*. 2008;115(4):409-415.
- Jellinger KA. A critical reappraisal of current staging of Lewy-related pathology in human brain. *Acta Neuropathol*. 2008;116(1):1-16.
- Zaccai J, Brayne C, McKeith I, Matthews F, Ince PG; MRC Cognitive Function, Ageing Neuropathology Study. Patterns and stages of alpha-synucleinopathy: relevance in a population-based cohort. *Neurology*. 2008;70(13):1042-1048.
- Burke RE, Dauer WT, Vonsattel JP. A critical evaluation of the Braak staging scheme for Parkinson's disease. *Ann Neurol*. 2008;64(5):485-491.
- Del Tredici K, Rub U, De Vos RA, Bohl JR, Braak H. Where does parkinson disease pathology begin in the brain? *J Neuropathol Exp Neurol*. 2002;61(5):413-426.
- Boeve BF, Dickson DW, Olson EJ, et al. Insights into REM sleep behavior disorder pathophysiology in brainstem predominant Lewy body disease. *Sleep Med*. 2007;8(1):60-64.
- Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol Aging*. 1997;18(4):351-357.
- Benedetti MD, Maraganore DM, Bower JH, et al. Hysterectomy, menopause, and estrogen use preceding Parkinson's disease: an exploratory case-control study. *Mov Disord*. 2001;16(5):830-837.
- Rocca WA, Bower JH, Maraganore DM, et al. Increased risk of parkinsonism in women who underwent oophorectomy before menopause. *Neurology*. 2008;70(3):200-209.
- Benedetti MD, Bower JH, Maraganore DM, et al. Smoking, alcohol, and coffee consumption preceding Parkinson's disease: a case-control study [comment]. *Neurology*. 2000;55(9):1350-1358.
- Shiba M, Bower JH, Maraganore DM, et al. Anxiety disorders and depressive disorders preceding Parkinson's disease: a case-control study. *Mov Disord*. 2000;15(4):669-677.
- Leibson CL, Maraganore DM, Bower JH, Ransom JE, O'Brien PC, Rocca WA. Comorbid conditions associated with Parkinson's disease: a population-based study. *Mov Disord*. 2006;21(4):446-455.
- Frigerio R, Elbaz A, Sanft KR, et al. Education and occupations preceding Parkinson disease: a population-based case-control study. *Neurology*. 2005;65(10):1575-1583.
- Bower JH, Maraganore DM, Peterson BJ, McDonnell SK, Ahlskog JE, Rocca WA. Head trauma preceding PD: a case-control study. *Neurology*. 2003;60(10):1610-1615.
- Frigerio R, Breteler MM, de Lau LM, et al; Mariza de Andrade. Number of children and risk of Parkinson's disease. *Mov Disord*. 2007;22(5):632-639.
- Ishizawa T, Mattila P, Davies P, Wang D, Dickson DW. Colocalization of tau and alpha-synuclein epitopes in Lewy bodies. *J Neuropathol Exp Neurol*. 2003;62(4):389-397.
- DelleDonne A, Klos KJ, Fujishiro H, et al. Incidental Lewy body disease and preclinical Parkinson disease. *Arch Neurol*. 2008;65(8):1074-1080.
- Dickson DW, Fujishiro H, DelleDonne A, et al. Evidence that incidental Lewy body disease is pre-symptomatic Parkinson's disease. *Acta Neuropathol*. 2008;115(4):437-444.
- Lin LI. A concordance correlation coefficient to evaluate reproducibility. *Biometrics*. 1989;45(1):255-268.
- Uchiyama M, Isse K, Tanaka K, et al. Incidental Lewy body disease in a patient with REM sleep behavior disorder. *Neurology*. 1995;45(4):709-712.
- Abbott RD, Ross GW, Petrovitch H, et al. Bowel movement frequency in late-life and incidental Lewy bodies. *Mov Disord*. 2007;22(11):1581-1586.
- Ross GW, Abbott RD, Petrovitch H, et al. Association of olfactory dysfunction with incidental Lewy bodies. *Mov Disord*. 2006;21(12):2062-2067.
- Beach TG, Adler CH, Sue LI, et al. Reduced striatal tyrosine hydroxylase in incidental Lewy body disease. *Acta Neuropathol*. 2008;115(4):445-451.
- Iwanaga K, Wakabayashi K, Yoshimoto M, et al. Lewy body-type degeneration in cardiac plexus in Parkinson's and incidental Lewy body diseases. *Neurology*. 1999;52(6):1269-1271.
- Orimo S, Uchihara T, Nakamura A, et al. Axonal alpha-synuclein aggregates herald centripetal degeneration of cardiac sympathetic nerve in Parkinson's disease. *Brain*. 2008;131(pt 3):642-650.
- Menza MA, Golbe LI, Cody RA, Forman NE. Dopamine-related personality traits in Parkinson's disease. *Neurology*. 1993;43(3, pt 1):505-508.
- Tomer R, Aharon-Peretz J. Novelty seeking and harm avoidance in Parkinson's disease: effects of asymmetric dopamine deficiency. *J Neurol Neurosurg Psychiatry*. 2004;75(7):972-975.
- Ishihara L, Brayne C. What is the evidence for a premorbid parkinsonian personality: a systematic review. *Mov Disord*. 2006;21(8):1066-1072.