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Incidental Lewy Body Disease: Clinical Comparison to a Control Cohort

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Abstract

Limited clinical information has been published on cases pathologically diagnosed with incidental Lewy body disease (ILBD). Standardized, longitudinal movement and cognitive data was collected on a cohort of subjects enrolled in the Sun Health Research Institute Brain and Body Donation Program. Of 277 autopsied subjects who had antemortem clinical evaluations within the previous 3 years, 76 did not have Parkinson's disease, a related disorder, or dementia of which 15 (20%) had ILBD. Minor extrapyramidal signs were common in subjects with and without ILBD. Cognitive testing revealed an abnormality in the ILBD group in the Trails B test only. ILBD cases had olfactory dysfunction; however, sample size was very small. This preliminary report revealed ILBD cases have movement and cognitive findings that for the most part were not out of proportion to similarly assessed and age-similar cases without Lewy bodies. Larger sample size is needed to have the power to better assess group differences.

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Keywords

incidental Lewy body disease; Lewy bodies; Parkinson's disease; demential with Lewy bodies

Incidental Lewy body disease (ILBD) describes autopsied individuals who have Lewy bodies or Lewy neurites without clinical findings of parkinsonism or dementia. It is estimated that up to 30% of autopsied individuals over age 65 have ILBD.[1–6] It is thought that ILBD may represent preclinical Parkinson's disease (PD) or dementia with Lewy bodies (DLB). ILBD has been associated with substantia nigra neuron degeneration,[7–9] reduction in tyrosine hydroxylase immunoreactivity,[10,11] and a reduction in vesicular monoamine transporter 2 (VMAT2).[9] These findings suggest that, during life, ILBD cases might have movement or cognitive findings that differentiate them from a control population. However, detailed clinical data from ILBD cases have been lacking. This study compared ILBD with non-ILBD cases in a brain donation program to determine whether ILBD cases showed extrapyramidal or cognitive signs that did not reach diagnostic criteria for PD or DLB.

PATIENTS AND METHODS

The Sun Health Research Institute (SHRI) Brain and Body Donation Program is an autopsy program that enrolls volunteer subjects from the community, as well as targeted patients with PD and Alzheimer's disease (AD), for standardized longitudinal antemortem clinical assessments until death.[12–14] All subjects signed informed consent approved by the SHRI IRB. At any given time there are approximately 500 subjects with and 500 subjects without a formal diagnosis of PD, AD, or other parkinsonian or dementing disorder enrolled in the cohort. The autopsy rate is ~70 autopsies per year and <10% of cases drop out of the study. From 1997 to 2008, 277 autopsied subjects had undergone at least one movement disorders examination (UPDRS, timed tap test, Purdue pegboard test) and a neuropsychological test battery prior to death. [14,15] Subjects meeting published criteria for PD or related disorders, or any type of dementia, were excluded from this analysis. A subset of cases had olfactory testing using the 40-point University of Pennsylvania Smell Identification Test.[16] Only autopsied subjects with antemortem testing within 3 years of death were included.

Neuropathological methods using a standardized series of brain regions stained with H&E as well as immunohistochemically for α-synuclein have been previously described.[10,12] A subject was categorized as being ILBD if there was Lewy synucleinopathy present and the subject had not met clinical criteria for the diagnosis of PD, other parkinsonian disorders, or dementia (including DLB). The Dementia with Lewy Bodies Consortium staging system[17] and the Unified Staging System for Lewy Body Disorders[18] were used to describe Lewy body stages. Brainstem regions included medulla, locus ceruleus, and substantia nigra; limbic regions included the nucleus basalis of Meynert, amygdala, transentorhinnal, and cingulate cortex.

Comparisons from the last examination prior to death were made for clinical diagnosis, Unified Parkinson's Disease Rating Scale (UPDRS) motor scores, timed tap, and pegboard test scores, and individual neuropsychological test scores using the two-sample *t* test or the Pearson χ^2 test. Additionally, comparisons for individual items in the UPDRS exam were made with two levels of abnormality defined: either a UPDRS score ≥1 or a more stringent UPDRS score ≥2. Adjusted means were compared by using a general linear model with terms for ILBD, age, and sex. Adjusted odds ratio (OR) were calculated by using multiple logistic regression with terms for ILBD, age, and sex. The noninferiority margin (operational definition of a clinically important difference) for comparisons of means was defined as 1 standard deviation (SD) of the levels for the control group. The noninferiority margin for comparisons of prevalence was

defined as an OR of 1.5. The confidence interval for Purdue pegboard, timed tap, and UPDRS III, AVLT, COWA, Stroop interference, and WAIS Digit Span scores did not include a 1 SD difference, and so the power was good for those comparisons. The conclusions are preliminary for the other comparisons that did not show a difference.

RESULTS

Of 277 autopsied cases, 76 met inclusion and exclusion criteria for diagnoses: 15 had ILBD and 61 were non-ILBD. Excluded cases may have had more than one exclusionary diagnosis and these included: 103 AD, 68 PD, 28 PSP, 21 other parkinsonian disorders, 17 vascular dementia, 16 DLB, and 9 other dementias. Two ILBD and six non-ILBD cases had not had any movement scores in the previous 3 years so were excluded from the movement analysis. Some (5 ILBD and 24 non-ILBD cases) did not have neuropsychological testing within 3 years of death so were excluded from cognitive analysis. Movement (Table 1 and Table 2) and cognitive testing (Table 1) are presented. The mean ± SD interval since the movement exam was 1.2 ± 0.8 years (range 0.15–2.8 years) for the ILBD group and 1.1 ± 0.7 years (0.02–2.7 years) for the non-ILBD group [not significant (NS)]. The mean interval since the neuropsychological exam was 1.8 ± 0.8 years (0.5–2.9 years) for the ILBD group and 1.1 ± 0.7 years (0.21–3.0 years) for the non-ILBD group (NS). Mean age and gender did not differ between groups (Table 1). Using the Unified Staging System for Lewy Body Disorders[18] for the 15 ILBD cases, the distribution was as follows: two olfactory bulb only, nine brainstem predominant, one limbic predominant, and three brainstem and limbic; no cases were neocortical. The distribution using DLB III criteria[17] was as follows: 10 had brainstem stage, 3 had limbic stage, and 2 could not be classified as they were olfactory bulb only.

There was no significant difference between the groups in the mean UPDRS motor score or in the peg-board or timed tap tests (Table 1). Mild to moderate motor findings were present in both groups, including tremor (action and rest), difficulty arising from a chair, and postural instability (Table 2). Essential tremor was common in both the groups (46% ILBD, 40% controls), as was the percentage of subjects having an abnormality in individual UPDRS tests (Table 2). The only significant difference between groups in the cognitive testing was slower performance on Trails B in the ILBD group (Table 1). No differences were found in multiple other neuropsychological tests (Table 1). Mean MMSE scores differed by less than two points.

Olfactory testing was performed on a subset of cases and the time between testing and death was 0.7 to 4.4 years (mean = 2.0 years; Table 1). Olfactory function was significantly reduced in the ILBD group (Table 1).

DISCUSSION

Limited clinical information is available regarding ILBD as most studies are from autopsy programs that do not perform standardized antemortem clinical evaluations. If any controls have been used for comparison, they were few. Although the study sample is small, the presented data represents 12 years of data collection and provides a starting point for future ILBD research. As ILBD may be critical to developing methods for the early detection of PD or DLB, this data reveal the widespread presence of movement and cognitive findings in ILBD and elderly individuals without Lewy bodies.[9–11]

Neuropathological and neurochemical changes have suggested that ILBD may be an early stage for PD or DLB. One study found substantia nigra neuron degeneration8 while another did not. 7 Dopamine levels were normal in one study,[19] but reduced tyrosine hydroxylase (TH) immunoreactivity was found in two studies.[10,]11 As TH is the rate-limiting step in dopamine synthesis, and dopamine loss is the hallmark of PD, the reduction in TH activity suggests ILBD

is an intermediate stage leading to PD or DLB. It has also been shown that there is a reduction in VMAT2 and neuronal loss in the substantia nigra of ILBD cases compared with controls. 9 The reductions in TH and VMAT2 in the ILBD cases were intermediate between control and PD cases and correlated with the degree of neuronal loss in the substantia nigra.9 These findings would suggest that ILBD subjects might have clinical findings that did not meet criteria for PD or dementia.

However, our data did not reveal many clinical differences between non-ILBD and ILBD groups. The data revealed that there are mild and even moderate degrees of movement abnormality, especially tremor, gait difficulty, and postural instability in the elderly (ILBD and non-ILBD subjects). Comparison with a non-ILBD population is therefore critical when investigating ILBD. The lack of a difference in UPDRS motor score is similar to a study of 29 ILBD cases, where total UPDRS scores were reported to be similar for ILBD and controls.[7] These data also support previous findings of more than 50% of elderly individuals over age 80 having at least one bradykinetic finding on exam.20

As there has been interest in determining whether ET or RLS may be risk factors or preclinical stages for PD, this study did not find ET or RLS to be more common in ILBD compared with controls. We had defined ET as subjects who had grade 2 postural or kinetic tremor of the hands or forearms without identifiable secondary cause or grade 1 tremor found over a period of ≥3 years.[21] Even when looking at the presence of action tremor, without classifying the subject as ET, there was no clear relationship with ILBD.

While detailed neuropsychological testing revealed a significant difference in performance on Trails B, no other test met statistical criteria for differing performance between the groups, although sample size is very small. Trails B is a measure of frontoexecutive function and this domain is often involved in the cognitive decline of patients with PD. This may reflect lower levels of striatal TH and potential dopamine activity in ILBD as we have previously found. [10] While this was the only cognitive test with a significant difference in the analysis, it may well support the recently published data which found mild cognitive impairment in ~20% of PD subjects at the time of initial diagnosis PD.[22] Further study and larger number of cases are needed to better determine whether cognitive dysfunction is present in ILBD.

The number of cases having olfactory testing was very small, but the finding of a marked decrease in UPSIT scores in the ILBD group is provocative and suggests that ILBD may be a premotor stage for PD. These data would support previously published studies of olfaction that identify an abnormality which predates motor PD.

This study has limitations. The number of ILBD subjects with complete examination data is small and expanding the ILBD case numbers is needed. While it may seem obvious that ILBD cases would not have parkinsonism or dementia (as cases that met published criteria for these disorders would have PD or DLB), there has been limited published data on ILBD clinical findings, especially in comparison to similarly assessed control subjects. This study included two ILBD cases that had Lewy bodies in the olfactory bulb only. The rest of the cases had brainstem and limbic Lewy body stage and none had neocortical Lewy body stage. Whether expanding the number of ILBD cases would result in different Lewy body stages and possibly differences in motor or cognitive testing differences is unclear.

Future work needs to focus on longitudinal changes in motor or cognitive findings in individual subjects. For example, if a subject has a specific reduction in motor or cognitive function on one or more tests over a defined period of time that may indicate the presence of a Lewy body disorder. Additionally, as Lewy body staging suggests initial involvement in non-CNS regions, as well as olfactory bulb, analysis of data regarding autonomic dysfunction, sleep disorders, and the olfactory testing may be more valuable as bio-markers for PD and DLB. Finally, if

synuclein ligands for positron emission tomography (PET) or single photon emissions tomography (SPECT) scanning can be produced, correlation of imaging with the clinical data and eventual autopsy findings of ILBD may result in a better understanding of this pathologic diagnosis.

In conclusion, this study provides some of the most detailed clinical (movement and cognitive) data on prospectively assessed subjects with ILBD. Notable motor and cognitive changes were not seen. While study size was small, investigators interested in ILBD can use this data for comparison purposes.

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REFERENCES

1. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51:745–752. [PubMed: 2841426]
2. Mayeux R, Marder K, Cote LJ, et al. The frequency of idiopathic Parkinson's disease by age, ethnic group, and sex in northern Manhattan, 1988–1993. Am J Epidemiol 1995;142:820–827. [PubMed: 7572958]
3. Saito Y, Ruberu NN, Sawabe M, et al. Lewy body-related α-synucleinopathy in aging. J Neuropathol Exp Neurol 2004;63:742–749. [PubMed: 15290899]
4. Bloch A, Probst A, Bissig H, Adams H, Tolnay M. α-Synuclein pathology of the spinal and peripheral autonomic nervous system in neurologically unimpaired elderly subjects. Neuropathol Appl Neurobiol 2006;32:284–295. [PubMed: 16640647]
5. Minguez-Castellanos A, Chamorro CE, Escamilla-Sevilla F, et al. Do α-synuclein aggregates in autonomic plexuses predate Lewy body disorders?: a cohort study. Neurology 2007;68:2012–2018. [PubMed: 17548551]
6. Jellinger KA. Lewy body-related α-synucleinopathy in the aged human brain. J Neural Transm 2004;111:1219–1235. [PubMed: 15480835]
7. Ross GW, Petrovitch H, Abbott RD, et al. Parkinsonian signs and substantia nigra neuron density in decendents elders without PD. Ann Neurol 2004;56:532–539. [PubMed: 15389895]
8. Fearnley JM, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain 1991;114:2283–2301. [PubMed: 1933245]
9. DelleDonne A, Klos KJ, Fujishiro H, et al. Incidental Lewy body disease and preclinical Parkinson disease. Arch Neurol 2008;65:1074–1080. [PubMed: 18695057]
10. Beach TG, Adler CH, Sue LI, et al. Reduced striatal tyrosine hydroxylase in incidental Lewy body disease. Acta Neuropathol 2008;115:445–451. [PubMed: 17985144]
11. Dickson DW, Fujishiro H, DelleDonne A, et al. Evidence that incidental Lewy body disease is pre-symptomatic Parkinson's disease. Acta Neuropathol 2008;115:437–444. [PubMed: 18264713]
12. Beach TG, Sue LI, Walker DG, et al. The Sun Health Research Institute Brain Donation Program: description and experience, 1987–2007. Cell Tissue Banking 2008;9:229–245.
13. Adler CH, Hentz JG, Sabbagh M, et al. Motor impairment in normal aging, clinically possible Parkinson's disease, and clinically probable Parkinson's disease: longitudinal evaluation of a cohort of prospective brain donors. Mov Disord 2004;19:11–18.
14. Caviness JN, Driver-Dunckley E, Connor DJ, et al. Defining mild cognitive impairment in Parkinson's disease. Mov Disord 2007;22:1272–1277. [PubMed: 17415797]
15. Adler CH, Hentz JG, Joyce JN, Beach T, Caviness JN. Motor impairment in normal aging, clinically possible Parkinson's disease, and clinically probable Parkinson's disease: longitudinal evaluation of a cohort of prospective brain donors. Parkinsonism Relat Disord 2002;9:103–110. [PubMed: 12473400]

16. Doty RL, Shaman P, Kimmelman CP, Dann MS. University of Pennsylvania Smell Identification Test: a rapid quantitative olfactory function test for the clinic. Laryngoscope 1984;94(2 Part 1):176–178. [PubMed: 6694486]

17. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863–1872. [PubMed: 16237129]

18. Beach TG, Adler CH, Lue L, et al. Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction. Acta Neuropathol 2009;117:613–634. [PubMed: 19399512]

19. Fernandez A, de Ceballos ML, Rose S, Jenner P, Marsden CD. Alterations in peptide levels in Parkinson's disease and incidental Lewy body disease. Brain 1996;119(Part 3):823–830. [PubMed: 8673494]

20. Prettyman R. Extrapyramidal signs in cognitively intact elderly people. Age Ageing 1998;27:557–560. [PubMed: 12675093]

21. Shill HA, Adler CH, Sabbagh MN, et al. Pathologic findings in prospectively ascertained essential tremor subjects. Neurology 2008;70(16 Part 2):1452–1455. [PubMed: 18413570]

22. Aarsland DM, Bronnick KP, Larsen JPM, Tysnes OBM, Alves GM. for the Norwegian ParkWest Study Group. Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest Study SYMBOL. Neurology 2009;72:1121–1126. [PubMed: 19020293]

TABLE 1

Movement, cognitive, olfactory comparisons*

	ILBD	Non-ILBD	95% CI
Age (yrs)	87.7 (3.3), 13	86.2 (5.9), 55	NA
Female (%)	38	51	NA
UPSIT	15.8 (7.1), 4	28.6 (4.3), 26	−17.5 to −6.9**
UPDRS III	8.3 (4.1), 13	8.8 (6.9), 55	−4.7 to 3.4
Purdue pegboard			
Bilateral	8.5 (1.6), 11	8.0 (1.7), 38	−0.3 to 1.9
Dominant	11.5 (2.2), 11	10.8 (1.9), 38	−0.3 to 2.2
Subordinate	10.1 (1.9), 11	10.6 (2.0), 40	−1.5 to 1.1
Timed tap			
Dominant	148 (29), 12	156 (36), 39	−30 to 18
Subordinate	128 (23), 12	138 (31), 40	−29 to 11
MMSE	27.2 (1.9), 10	28.7 (1.4), 37	−2.2 to 0.0
AVLT total learning	36.1 (8.4), 9	40.8 (9.9), 37	−8.7 to 5.7
AVLT delayed recall	60 (30), 9	74 (35), 37	−33 to 21
Clock drawing	8.4 (1.7), 9	9.3 (0.9), 36	−1.8 to 0.0
Animal fluency	15.9 (5.0), 10	15.2 (3.9), 37	−1.6 to 4.5
Controlled Oral Word Association, total	31 (11), 10	37 (11), 37	−13 to 3
Stroop interference	−6.2 (4,1), 8	−5.8 (6.6), 33	−3.6 to 5.9
Trails A	54 (15), 10	43 (13), 34	−2 to 17
Trails B	198 (69), 10	114 (46), 34	33 to 112**
WAIS-III Digit Span	14.4 (2.5), 9	16.7 (3.6), 34	−4.7 to 0.9

* Data presented are mean (SD), N except for gender.

** $P \leq 0.001$.

TABLE 2

Movement examination abnormalities using UPDRS scores and other diagnoses

	ILBD	Control	Adjusted OR	95% CI
N	13	55	NA	NA
ET; n (%)	6 (46%)	22 (40%)	1.23	0.36–4.2
RLS; n (%)	1 (8%)	4 (7%)	0.97	0.10–9.6
Abnormality ≥ 1; n (%)				
Speech	5 (38%)	10 (18%)	2.8	0.75–11
Rest tremor	4 (31%)	18 (33%)	0.86	0.23–3.2
Action tremor	11 (85%)	31 (56%)	4.4	0.89–22
Finger taps	2 (15%)	18 (33%)	0.42	0.08–2.2
Hand movement	3 (23%)	18 (33%)	0.60	0.15–2.5
RAM of hands	3 (23%)	11 (20%)	1.33	0.30–5.9
Leg agility	4 (31%)	15 (27%)	1.08	0.28–4.2
Arising from chair	7 (54%)	27 (49%)	1.08	0.29–3.9
Gait	7 (54%)	23 (42%)	1.36	0.37–5.0
Postural stability	8 (62%)	36 (65%)	0.70	0.19–2.6
Abnormality ≥ 2; n (%)				
Speech	0	2 (4%)	NA	NA
Rest tremor	0	3 (5%)	NA	NA
Action tremor	4 (31%)	14 (25%)	1.33	0.35–5.1
Finger taps	2 (15%)	4 (7%)	2.85	0.43–19
Hand movement	2 (15%)	4 (7%)	2.4	0.38–15
RAM of hands	0	3 (5%)	NA	NA
Leg agility	0	6 (11%)	NA	NA
Arising from chair	4 (31%)	19 (35%)	0.81	0.21–3.2
Gait	2 (15%)	11 (20%)	0.70	0.13–3.8
Postural stability	7 (54%)	28 (51%)	1.09	0.31–3.8