Published in final edited form as:

Neurobiol Aging. 2011 May ; 32(5): 857–863. doi:10.1016/j.neurobiolaging.2009.05.019.

Incidental Lewy Body Disease: Do some cases represent a preclinical stage of Dementia with Lewy Bodies?

Roberta Frigerio^a, Hiroshige Fujishiro^b, Tae-Beom Ahn^b, Keith A. Josephs^a, Demetrius M. Maraganore^a, Anthony DelleDonne^b, Joseph E. Parisi^c, Kevin J. Klos^d, Bradley F. Boeve^a, Dennis W. Dickson^b, and Eric J. Ahlskog^{a,*}

^aDepartment of Neurology, Mayo Clinic, Rochester, MN, United States

^bDepartment of Neuroscience, Mayo Clinic, Jacksonville, FL, United States

^cDepartment of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, United States

^dThe Movement Disorder Clinic of Oklahoma, Tulsa, OK, United States

Abstract

Lewy pathology occurs in 8–17% of neurologically-normal people >age 60, termed incidental Lewy body disease, (iLBD). It is often assumed to represent preclinical Parkinson disease (PD). However, some iLBD cases have diffuse pathology inconsistent with preclinical PD. We analyzed iLBD cases (α -synuclein immunohistochemistry) using the Braak PD staging scheme and determined if some had a neuropathological pattern suggestive of preclinical Dementia with Lewy bodies (DLB). Of the 235 brains examined, 34 had iLBD (14.5%) and all but one could be assigned a Braak PD stage. The distribution of α -synuclein pathology in the 33 cases fell into three patterns: (1) Diffuse cortical and subcortical α -synuclein pathology; (2) No cortical α -synuclein pathology, but a caudal-to-rostral ascending pattern, primarily involving brainstem; (3) Intermediate between these two categories. Also, 6/33 cases failed to follow the pattern of contiguous spread proposed by Braak. These findings suggest dichotomy in the distribution of iLBD: some cases fit the Braak ascending scheme, conceptually consistent with preclinical PD, whereas others displayed prominent cortical involvement that might represent preclinical DLB.

Keywords

incidental Lewy body disease; parkinson disease; dementia with Lewy bodies

© 2009 Elsevier Inc. All rights reserved.

*Corresponding author: J. Eric Ahlskog, PhD, MD, Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, eahlskog@mayo.edu, Phone 1 507 284 2511, Fax 1 507 538 6012.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosures

Dr. Frigerio reports no disclosures; Dr. Fujishiro reports no disclosures; Dr. Ahn reports no disclosures; Dr. Josephs reports no disclosures; Dr. Maraganore reports a provisional application for patent under 37 CFR § 1.53 (c) entitled "Predicting Parkinson's Disease." No monies have been awarded to date. Dr. Maraganore also reports a provisional application for 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. DelleDonne reports no disclosures; Dr. Parisi reports no disclosures; Dr. Klos reports no disclosures; Dr. Boeve reports grant support from Myriad Pharmaceuticals and Honorarium from GE Healthcare; Dr. Dickson reports no disclosures; Dr. Ahlskog reports no disclosures.

1. Introduction

Deposits of α -synuclein in Lewy bodies (LBs) or Lewy neurites (LNs) in the central, peripheral and autonomic nervous system are the histopathologic hallmarks of both Parkinson disease (PD)(Braak et al., 2006; Braak et al., 2003; Braak et al., 2004; Braak et al., 2007) and dementia with LBs (DLB).(Lippa et al., 2007; McKeith et al., 2005) On the other hand, 8% to 17% of neurologically normal people over age 60 years have LBs on postmortem examination,(Bloch et al., 2006; Gibb and Lees, 1988; Klos et al., 2006) a process termed incidental Lewy body disease (iLBD).

iLBD is assumed to represent preclinical PD, and that premise has recently led to major revisions in our conceptualization of PD initiation and progression. Based on iLBD cases as well as clinically definite PD cases, Braak et al. developed a neuropathological staging scheme for PD and proposed that PD primarily starts in the caudal brainstem, with rostral spread of pathology over time. (Braak et al., 2006; Braak et al., 2003; Braak et al., 2004; Braak et al., 2007) This evolution of α -synuclein pathology is proposed to progress over six successive caudal-to-rostral stages: 1) lower medulla with involvement of the dorsal motor nucleus of the vagus nerve (but also olfactory bulb); 2) locus coeruleus; 3) substantia nigra and amygdala; 4) mesocortex; 5) temporal and prefrontal neocortex; 6) primary neocortex. Classic parkinsonism is not predicted to manifest until the middle stages, when the substantia nigra is affected. At the other end of the spectrum, cases of advanced PD with dementia (PDD) typically have Braak PD stages 5 or 6 with involvement of limbic cortex and neocortex.(Aarsland et al., 2005; Apaydin et al., 2002; Emre et al., 2007; Hurtig et al., 2000)

In some autopsy series DLB is the second leading cause of dementia and typically has nearly identical neuropathology to PDD, especially in DLB patients with overt parkinsonism. (Aarsland et al., 2004; Tsuboi and Dickson, 2005) Among DLB patients, however, dementia occurs early, and by definition, not more than a year after motor symptoms.(McKeith et al., 2005) By contrast, and as defined, dementia in PDD occurs at least one year after motor symptom onset. Of note, Braak staging incorporates iLBD as a precursor to PD or PDD, whereas there is no scheme for the pre-symptomatic neuropathological precursor for DLB.

Several studies have reported exceptions to Braak PD staging.(Beach et al 2009; Bloch et al., 2006; Halliday et al., 2008; Jellinger, 2003; Jellinger, 2008; Kalaitzakis et al., 2008; Parkkinen et al., 2005; Parkkinen et al., 2008; Zaccai et al., 2008) There is no consensus about how these should be addressed, although a recent paper suggests major revisions in the staging scheme.(Beach et al., 2009) The aim of this study was to review the distribution of LBs in subjects with iLBD, to analyze the validity of the Braak PD staging scheme, and perhaps extend it, as appropriate. We selected only post-mortem cases that had been devoid of clinical evidence of neurodegenerative disease or tremor in life, based on retrospective medical records review. The straight-forward prediction of the Braak scheme is that asymptomatic patients with LBs should be confined to early or middle stages.

2. Methods

2.1 Study subjects

We employed the Tissue Registry of the Mayo Clinic Rochester Epidemiology Project to retrospectively identify subjects from Olmsted County, MN, and the immediate vicinity that died between 1988–2004 with available brain autopsy tissues plus adequate Mayo medical records to document the absence of symptoms, signs or medical diagnosis of neurodegenerative disorders. Specifically, our inclusion criteria were: (a) age >60 years at death; (b) medical record documentation of at least one medical evaluation during the last

year of life. Our exclusion criteria were: (a) medical record documentation of parkinsonism, tremor, dementia, or other neurodegenerative disorders; (b) medical record documentation of large structural brain lesions that might have interfered with the post-mortem assessment (e.g., massive hemorrhage or stroke; large brain tumors).

2.2 Medical records abstraction

Medical records were obtained using the medical records linkage system of the Rochester Epidemiology Project. We reviewed the contents of all outpatient and inpatient medical notes, with data abstracted blinded to the neuropathological findings.

2.3 Neuropathological methods

Sections were taken from middle frontal (MF), superior temporal (ST), entorhinal and cingulate cortices, hippocampus, amygdala, basal nucleus of Meynert, midbrain, pons and medulla, as well as spinal cord. Olfactory bulb tissue was not available in our subjects.

To evaluate Alzheimer type pathology, senile plaques (SPs) and neurofibrillary tangles (NFTs) were counted in 3 cortical sections and in the hippocampus with thioflavin-S fluorescent microscopy. A Braak NFT stage and SP score was assigned to all cases based on the distribution of NFTs and SPs with thioflavin-S fluorescent microscopy. (Braak and Braak, 1991) The final neuropathologic diagnosis was made according to the National Institute on Aging-Reagan criteria for AD. (Hyman and Trojanowski, 1997)

To assess Lewy-related pathology sections were immunostained on a DAKO Autostainer with a polyclonal antibody to α -synuclein (1:3000; NACP98(Gwinn-Hardy et al., 2000)) as noted in a recent comparative study.(Beach et al., 2008b) The sections were pretreated with 95% formic acid and steamed in distilled water before immunohistochemistry.

The number of α -synuclein immunoreactive perikaryal LBs was counted in microscopic fields at x200 magnification in the amygdala, the basal nucleus of Meynert, the limbic cortex (entorhinal and cingulate cortices) and neocortex (superior temporal and middle frontal gyri), substantia nigra, locus ceruleus and dorsal motor nucleus of vagus. The highest number was obtained in one magnification field of the locus ceruleus and dorsal motor nucleus of vagus and scored from 0 to 3: 0 = absent, 1 = (1), 2 = (2), 3 = (3–5), 4 = (6). In other regions, three magnification fields with highest number of pathologies were selected and the average number of their values was calculated and scored from 0 to 4: 0 = absent, 1 = (0–1), 2 = (1–2), 3 = (3–5), 4 = (6). The degree of α -synuclein immunoreactive extra-perikaryal deposits, including LNs, intraneuritic LBs and dot-like neurites,(Saito et al., 2003) were graded from 0 to 3: 0 = absent, 1 = rare, 2 = some, 3 = many; 4 = numerous. All neuropathological assessments were blinded to the results of medical records abstraction.

Although only deceased subjects were included in this retrospective study (no risks to human subjects), all aspects of the study were approved by the Mayo Institutional Review Board.

3. Results

Of the 235 subjects initially analyzed in this study, 130 were women (55.3%). ILBD was neuropathologically documented in 34 subjects (14.5%), defined by the presence of α -synuclein immunoreactive neuronal or neuritic lesions in one or more selected brain regions. Of these iLBD cases, 18 (52.9%) were women, which was a slightly lower percentage than among the 235 total subjects. The median age at death of the iLBD cases was 82, ranging from 62–103 years. All iLBD cases had Mayo medical records dating back at least five years pre-mortem, with a median 20 physician visits during those last 5 years (25th

percentile = 12; 75th percentile = 24 visits/last 5 years). The mean duration of medical records among these iLBD patients was 48 years (range, 5–74).

Of the 34 iLBD cases, the distribution of α -synuclein pathology in 12 cases was consistent with Braak PD stages 5 or 6, including involvement of cingulate, superior temporal or mid-frontal cortices; notably however, the density of cortical Lewy-related pathology was sparse (see Figure). Among the remainder, 11 cases fit with Braak stages 1 to 3 (Stage 1 = 2 cases; Stage 2 = 3 cases; Stage 3 = 6 cases). An intermediate group included 10 cases; of these, nine were classified as Braak Stage 4, whereas α -synuclein pathology in the other was confined to two regions: locus ceruleus and superior temporal cortex. Finally, one subject had minimal LNs in the nucleus basalis of Meynert, but no other Lewy-related pathology, which defied Braak classification and was excluded from further analysis.

The 33 iLBD cases could be divided into three categories based on Braak PD stage, as shown in Table 1. The first group, characterized as “Ascending”, fits with PD staging scheme proposed by Braak, with α -synuclein pathology confined to brainstem and spinal cord (plus a single case that also included nucleus basalis pathology). This group also fits with the Kosaka classification of “brainstem predominant.” (Kosaka et al., 1984) At the other end of the spectrum (Table 1) were the 12 cases of widespread involvement, including cortical α -synuclein pathology, a finding expected for advanced PD (Braak Stages 5–6) or Kosaka’s categories of “limbic/transitional” or “diffuse neocortical.” (Kosaka et al., 1984) We have chosen to characterize this group as “Diffuse” (Table 1). Finally, 10 cases were in between these two categories, and classified as “Intermediate” in Table 1; thus, α -synuclein pathology could have placed these cases into either of the two other categories.

Lewy body and neurite counts in each of the three brainstem nuclei (dorsal motor nucleus of the vagus, locus ceruleus and substantia nigra) were consistently greater in the Diffuse group compared to the Ascending group; the Intermediate group’s counts were in between. Thus, the Diffuse group not only had most widespread Lewy pathology, but also the highest Lewy counts in every analyzed region.

Among the iLBD cases, six did not fit with a continuous caudal-to-rostral spread of pathology according to the Braak scheme; i.e., there were skipped regions. This included four cases where the dorsal motor nucleus of the vagus was spared. Of these six cases, five were in the Intermediate group and one in the Ascending group. Thus, 21% of all the iLBD cases failed to display a contiguous ascending pattern, if we also include the single case that had LNs only in basal nucleus of Meynert.

Table 2 summarizes the burden of Alzheimer type pathology in the 33 iLBD cases, including Braak NFT stages, CERAD SP score, and NIA-Reagan Alzheimer scores. The NIA-Reagan scores were all 0–2, with “2” representing intermediate probability of AD; this relatively low NIA-Reagan score was not unexpected, given our pre-mortem clinical exclusion criterion of dementia. There was no association of iLBD pathology and Alzheimer type pathology. Table 2 also summarizes the median ages at death and gender distributions by group.

4. Discussion

There is a working assumption that iLBD represents an early stage in the PD neurodegenerative process, either as a precursor or an aborted pathological state. Indeed, iLBD cases have striatal dopaminergic deficits consistent with this assumption. (Beach et al., 2008a; DelleDonne et al., 2008) In fact, a presymptomatic state is a necessary assumption given the known slow progression of PD, plus the fact that symptoms develop only after substantial neuronal damage.

This begs the question of the presymptomatic pathological substrate for the other major Lewy body disorder, DLB. DLB manifests with symptoms referable to cortex (i.e. dementia), but usually with concurrent parkinsonism. This issue is directly relevant to the current findings where a substantial proportion of our iLBD cases had α -synuclein pathology affecting one or more cortical regions, although the density of pathology was considerably less than in similar stage cases with clinically overt DLB. (Fujishiro et al., 2008) Thus, although approximately a third of our cases had isolated brainstem α -synuclein pathology (consistent with premotor PD), another third had neuropathology that one might predict is a precursor to DLB (i.e. Braak PD stages 5–6). The remaining third of our cases were in between, and could arbitrarily be placed into one or the other category. Also consistent with a pre-DLB state, Parkkinen, et al. (Parkkinen et al., 2008) noted that about half of their Braak Stage 5–6 cohort was asymptomatic, similar to our Diffuse group in Table 1. Restated, we propose that iLBD is dichotomous, with some cases representing the earliest stage of PD (or eventually PDD), and others, DLB. Whether each reflects a preclinical, precursor stage, or a state where the pathogenic process has been aborted or compensated remains to be determined.

Fully developed DLB may manifest as one of two neuropathological phenotypes: (1) diffuse cortical LBs with concurrent Alzheimer type pathology (NIA-Reagan intermediate to high); (2) minimal or no Alzheimer type pathology (NIA-Reagan low) and either transitional or diffuse cortical LBs. (Fujishiro et al., 2008) Our Diffuse, asymptomatic cases may primarily represent the precursor to the latter type of DLB, since they had limited Alzheimer type pathology.

We identified no cases where Lewy-related pathology was predominantly in the amygdala (Leverenz, et al, 2008), a common form of α -synuclein pathology in the setting of advanced AD. (Uchikado et al., 2006) The amygdala is the nucleus that is most consistently affected among cases with concurrent AD pathology. (Hamilton, 2000) Since the NIA-Reagan scores for all of our cases was 0–2 (no more than intermediate AD probability), the absence of amygdala-predominant Lewy-related pathology is not surprising. Parenthetically, the reason for the relatively low NIA-Reagan scores in these cases likely relates to the careful screening of medical records and exclusion of cases with documented cognitive impairment.

Consistent with multiple prior studies, (Bloch et al., 2006; Halliday et al., 2008; Jellinger, 2003; Jellinger, 2008; Kalaitzakis et al., 2008; Parkkinen et al., 2005; Parkkinen et al., 2008; Zaccai et al., 2008) we noted a minority of cases (21%) where the topographical caudal-to-rostral continuity of the Braak PD staging scheme was violated. This is not crucial to the Braak scheme, per se; however, it has implications for the proposal that a neurotrophic pathogen, such as a virus, ascends from gut or descends from olfactory bulb. (Hawkes et al., 2007) Obviously, such a transsynaptically traveling pathogen might not leave evidence at every level, accounting for the skipped regions. Or, we and others might have missed Lewy pathology that would have been detected with intensive serial sectioning through all the relevant nuclei. On the other hand, there is not much of a precedent for such a process playing a role in neurodegenerative disease.

Skipped regions in the Braak PD scheme also suggest that the underlying pathogenic process may be multifocal in origin, rather than starting from one or two regions (e.g. dorsal motor nucleus or olfactory bulb), and subsequently ascending or descending. This pathological evidence, in the aggregate, would suggest a multifocal initiation as the more likely pathogenic scenario, and this has recently been emphasized. (Burke et al., 2008)

One might take a different view of these data and argue that Braak PD staging has no validity and that the concept of an ascending caudal-to-rostral evolution of PD pathology

should be abandoned; this view has recently gotten traction.(Burke et al., 2008) However, the Braak caudal-to-rostral scheme does have support, although not necessarily with the precise neuroanatomic contiguity initially postulated. Thus, prior work has documented that clinically-established PD without dementia largely spares limbic cortex and neocortex, whereas advanced PD patients of similar age, but with levodopa-refractory motor syndromes and dementia, have transitional or neocortical Lewy-related pathology.(Apaydin et al., 2002) Other investigations similarly support the proposal that PDD differs from PD without dementia by way of Lewy-related cortical pathology. (Aarsland et al., 2005; Hurtig et al., 2000) Pathological assessment stratified by PD duration also suggests an ascending process not simply explained by age; thus, short PD durations are associated with primarily brainstem pathology, whereas much longer PD durations include Lewy-related pathology at higher levels.(Halliday et al., 2008)

The widespread Lewy-related pathology (Braak Stages 5–6) among some of our patients, as well as those in other studies(Parkkinen et al., 2008; Zaccai et al., 2008) obviously does not necessarily imply clinical consequences. LBs and LNs are markers of a disease process, but in the context of iLBD, may not necessarily reflect neuronal dysfunction, which in some cases may be minimal, compensated or controlled. Clinical symptoms in neurodegenerative disease presumably correlate with loss of neurons and perhaps more importantly synapses. (Kramer and Schultz-Schaeffer, 2007; Terry, 2000) However, comparative assessment of synapse and neuronal loss is extremely laborious and fraught with methodologic issues; hence, the nearly universal reliance on Lewy-related pathology, per se, to mark PD stages.

One possible criticism is the potential for case selection bias that is common among post-mortem investigations. However, not only were the iLBD cases identified blinded to the clinical data, they were derived from a large cohort of seniors dying without evidence of neurodegenerative disease; thus, selection bias relevant to the outcomes should not be substantial. Note also that autopsy rates for our local population are nearly twice the national average.(Nemetz et al., 1989; Nemetz et al., 1987)

This investigation also may be criticized for the retrospective design that is nearly universal among iLBD series. Obviously, without a comprehensive neurologic examination shortly before death, there can be no assurance of complete neurologic normality among the iLBD cases. However, to accomplish this with a prospective design would be extremely labor-intensive, require up to two decades to complete, and prohibitively expensive. Tending to offset this concern, the Mayo medical records were detailed, spanned a minimum of 5 years before death in our iLBD cases, and with the stipulation that all patients had been evaluated by a Mayo physician within the last year (median 20 physician visits the last 5 years). A neurologist, blinded to the neuropathological diagnoses, confirmed medical record-absence of dementia, tremor, parkinsonism or other evidence of neurodegenerative disease. Moreover, the incidence of iLBD in our series (14.5%) is nearly ten times greater than the lifetime risk (1.6%) for PD in the Olmsted County population.(Elbaz et al., 2002) Thus, although mild parkinsonism, tremor or cognitive impairment could have been overlooked, this highly disproportionate frequency of iLBD suggests that most of these cases were not simply undetected PD.

In conclusion, two points deserve reiteration. First, incidental, but diffuse Lewy-related pathology (Braak PD stages 5–6) is a plausible precursor to DLB. Neurodegenerative disorders do not start abruptly and a preclinical pathological state is expected. This complements the current Braak PD staging scheme, which as currently written, is directly applicable only to PD. Second, we and other investigators have documented iLBD cases where brain regions that are integral to the ascending Braak scheme were skipped; this is contrary to the proposal of a neurotrophic pathogen passing transsynaptically.(Braak et al.,

2006; Hawkes et al., 2007) The exceptions suggest that the beginnings of PD may reflect multifocal susceptibility, as has recently been emphasized, (Burke et al., 2008) rather than one to two regions of origin.

Acknowledgments

The authors thank Mike Oelkers and Connie McDonough for help with the Tissue Registry, and Monica Casey-Castanedes, Virginia Phillips and Linda Rousseau for histological technical support. The study was supported by the Morris K. Udall Parkinson's Disease Research Center of Excellence grant (P50 NS40256), by the NIH grant 2R01 ES10751, by the Mayo Alzheimer's Disease Research Center (P50 AG16754), and by the Mayo Alzheimer's Disease Patient Registry (U01 AG06786).

References

- Aarsland D, Ballard CG, Halliday G. Are Parkinson's disease with dementia and dementia with Lewy bodies the same entity? *J. Geriatr. Psychiatry Neurol.* 2004; 17:137–145. [PubMed: 15312277]
- Aarsland D, Perry R, Brown A, Larsen JP, Ballard C. Neuropathology of dementia in Parkinson's disease: a prospective, community-based study. *Ann. Neurol.* 2005; 58:773–776. [PubMed: 16240351]
- Apaydin H, Ahlskog JE, Parisi JE, Boeve BF, Dickson DW. Parkinson disease neuropathology: later-developing dementia and loss of the levodopa response. *Arch. Neurol.* 2002; 59:102–112. [PubMed: 11790237]
- Beach TG, Adler CH, Sue LI, Peirce JB, Bachalakuri J, Dalsing-Hernandez JE, Lue LF, Caviness JN, Connor DJ, Sabbagh MN, Walker DG. Reduced striatal tyrosine hydroxylase in incidental Lewy body disease. *Acta Neuropathol.* 2008b; 115:445–451. [PubMed: 17985144]
- Beach TG, White CL, Hamilton RL, Duda JE, Iwatsubo T, Dickson DW, Leverenz JB, Roncaroli F, Buttini M, Hladik CL, Sue LI, Noorigian JV, Adler CH. Evaluation of alpha-synuclein immunohistochemical methods used by invited experts. *Acta Neuropathol.* 2008b; 116:277–288. [PubMed: 18626651]
- Beach TG, Adler CH, Lue L, Sue LI, Bachalakuri J, Henry-Watson J, Sasse J, Boyer S, Shirobi S, Brooks R, Eschbacher J, White CL 3rd, Akiyama H, Caviness J, Shill HA, Connor DJ, Sabbagh MM, Walker DG. THE Arizona Parkinson's Disease Consortium. Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction. *Acta Neuropathol.* 2009 Apr 28.
- 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; 32:284–295. [PubMed: 16640647]
- Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol.* 1991; 82:239–259. [PubMed: 1759558]
- 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; 396:67–72. [PubMed: 16330147]
- 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; 24:197–211. [PubMed: 12498954]
- 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; 318:121–134. [PubMed: 15338272]
- 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; 113:421–429. [PubMed: 17294202]
- Burke RE, Dauer WT, Vonsattel JP. A critical evaluation of the Braak staging scheme for Parkinson's disease. *Ann. Neurol.* 2008; 64:485–491. [PubMed: 19067353]
- DelleDonne A, Klos KJ, Fujishiro H, Ahmed Z, Parisi JE, Josephs KA, Frigerio R, Burnett M, Wszolek ZK, Uitti RJ, Ahlskog JE, Dickson DW. Incidental Lewy body disease and preclinical Parkinson disease. *Arch. Neurol.* 2008; 65:1074–1080. [PubMed: 18695057]

- Elbaz A, Bower JH, Maraganore DM, McDonnell SK, Peterson BJ, Ahlskog JE, Schaid DJ, Rocca WA. Risk tables for parkinsonism and Parkinson's disease. *J. Clin. Epidemiol.* 2002; 55:25–31. [PubMed: 11781119]
- Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, Broe GA, Cummings J, Dickson DW, Gauthier S, Goldman J, Goetz C, Korczyn A, Lees A, Levy R, Litvan I, McKeith I, Olanow W, Poewe W, Quinn N, Sampaio C, Tolosa E, Dubois B. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov. Disord.* 2007; 22:1689–1707. [PubMed: 17542011]
- Fujishiro H, Ferman TJ, Boeve BF, Smith GE, Graff-Radford NR, Uitti RJ, Wszolek ZK, Knopman DS, Petersen RC, Parisi JE, Dickson DW. Validation of the neuropathologic criteria of the third consortium for dementia with Lewy bodies for prospectively diagnosed cases. *J. Neuropathol. Exp. Neurol.* 2008; 67:649–656. [PubMed: 18596548]
- 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]
- Gwinn-Hardy K, Mehta ND, Farrer M, Maraganore D, Muentner M, Yen SH, Hardy J, Dickson DW. Distinctive neuropathology revealed by alpha-synuclein antibodies in hereditary parkinsonism and dementia linked to chromosome 4p. *Acta Neuropathol. (Berl.).* 2000; 99:663–672. [PubMed: 10867800]
- Halliday G, Hely M, Reid W, Morris J. The progression of pathology in longitudinally followed patients with Parkinson's disease. *Acta Neuropathol.* 2008; 115:409–415. [PubMed: 18231798]
- Hamilton RL. Lewy bodies in Alzheimer's disease: a neuropathological review of 145 cases using alpha-synuclein immunohistochemistry. *Brain Pathol.* 2000; 10:378–384. [PubMed: 10885656]
- Hawkes CH, Del Tredici K, Braak H. Parkinson's disease: a dual-hit hypothesis. *Neuropathol. Appl. Neurobiol.* 2007; 33:599–614. [PubMed: 17961138]
- Hurtig HI, Trojanowski JQ, Galvin J, Ewbank D, Schmidt ML, Lee VM, Clark CM, Glosser G, Stern MB, Gollomp SM, Arnold SE. Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease. *Neurology.* 2000; 54:1916–1921. [PubMed: 10822429]
- Hyman BT, Trojanowski JQ. Consensus recommendations for the postmortem diagnosis of Alzheimer disease from the National Institute on Aging and the Reagan Institute Working Group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. *J. Neuropathol. Exp. Neurol.* 1997; 56:1095–1097. [PubMed: 9329452]
- Jellinger KA. Alpha-synuclein pathology in Parkinson's and Alzheimer's disease brain: incidence and topographic distribution--a pilot study. *Acta Neuropathol.* 2003; 106:191–201. [PubMed: 12845452]
- Jellinger KA. A critical reappraisal of current staging of Lewy-related pathology in human brain. *Acta Neuropathol.* 2008; 116:1–16. [PubMed: 18592254]
- Kalaitzakis ME, Graeber MB, Gentleman SM, Pearce RK. The dorsal motor nucleus of the vagus is not an obligatory trigger site of Parkinson's disease: a critical analysis of alpha-synuclein staging. *Neuropathol. Appl. Neurobiol.* 2008; 34:284–295. [PubMed: 18053026]
- Klos KJ, Ahlskog JE, Josephs KA, Apaydin H, Parisi JE, Boeve BF, DeLucia MW, Dickson DW. Alpha-synuclein pathology in the spinal cords of neurologically asymptomatic aged individuals. *Neurology.* 2006; 66:1100–1102. [PubMed: 16606927]
- Kosaka K, Yoshimura M, Ikeda K, Budka H. Diffuse type of Lewy body disease: progressive dementia with abundant cortical Lewy bodies and senile changes of varying degree--a new disease? *Clin. Neuropathol.* 1984; 3:185–192. [PubMed: 6094067]
- Kramer ML, Schulz-Schaeffer WJ. Presynaptic alpha-synuclein aggregates, not Lewy bodies, cause neurodegeneration in dementia with Lewy bodies. *J Neurosci.* 2007; 27:1405–1410. [PubMed: 17287515]
- Leverenz JB, Hamilton R, Tsuang DW, Schantz A, Vavrek D, Larson EB, Kukull WA, Lopez O, Galasko D, Masliah E, Kaye J, Woltjer R, Clark C, Trojanowski JQ, Montine TJ. Empiric refinement of the pathologic assessment of Lewy-related pathology in the dementia patient. *Brain Pathol.* 2008; 18:220–224. [PubMed: 18241240]
- Lippa CF, Duda JE, Grossman M, Hurtig HI, Aarsland D, Boeve BF, Brooks DJ, Dickson DW, Dubois B, Emre M, Fahn S, Farmer JM, Galasko D, Galvin JE, Goetz CG, Growdon JH, Gwinn-Hardy KA, Hardy J, Heutink P, Iwatsubo T, Kosaka K, Lee VM, Leverenz JB, Masliah E, McKeith IG,

- Nussbaum RL, Olanow CW, Ravina BM, Singleton AB, Tanner CM, Trojanowski JQ, Wszolek ZK, DLB/PDD WorkingGroup. DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers. *Neurology*. 2007; 68:812–819. [PubMed: 17353469]
- McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA, Korczyn A, Kosaka K, Lee VM, Lees A, Litvan I, Londos E, Lopez OL, Minoshima S, Mizuno Y, Molina JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schultz JB, Trojanowski JQ, Yamada M. Consortium on DLB Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005; 65:1863–1872. [PubMed: 16237129]
- Nemetz PN, Ballard DJ, Beard CM, Ludwig J, Tangalos EG, Kokmen E, Weigel KM, Belau PG, Bourne WM, Kurland LT. An anatomy of the autopsy, Olmsted County, 1935 through 1985. *Mayo Clin. Proc.* 1989; 64:1055–1064. [PubMed: 2811484]
- Nemetz PN, Ludwig J, Kurland LT. Assessing the autopsy. *Am. J. Pathol.* 1987; 128:362–379. [PubMed: 3113257]
- Parkkinen L, Kauppinen T, Pirttila T, Autere JM, Alafuzoff I. Alpha-synuclein pathology does not predict extrapyramidal symptoms or dementia. *Ann. Neurol.* 2005; 57:82–91. [PubMed: 15562510]
- Parkkinen L, Pirttila T, Alafuzoff I. Applicability of current staging/categorization of alpha-synuclein pathology and their clinical relevance. *Acta Neuropathol.* 2008; 115:399–407. [PubMed: 18297293]
- Saito Y, Kawashima A, Ruberu NN, Fujiwara H, Koyama S, Sawabe M, Arai T, Nagura H, Yamanouchi H, Hasegawa M, Iwatsubo T, Murayama S. Accumulation of phosphorylated alpha-synuclein in aging human brain. *J. Neuropathol. Exp. Neurol.* 2003; 62:644–654. [PubMed: 12834109]
- Terry RD. Cell death or synaptic loss in Alzheimer disease. *J. Neuropathol. Exp. Neurol.* 2000; 59:1118–1119. [PubMed: 11138931]
- Tsuboi Y, Dickson DW. Dementia with Lewy bodies Parkinson's disease with dementia: are they different? *Parkinsonism. Relat. Disord.* 2005; 11(Suppl 1):S47–S51. [PubMed: 15885629]
- Uchikado H, Lin WL, DeLucia MW, Dickson DW. Alzheimer disease with amygdala Lewy bodies: a distinct form of alpha-synucleinopathy. *J Neuropathol Exp Neurol.* 2006; 65:685–697. [PubMed: 16825955]
- Zaccai J, Brayne C, McKeith I, Matthews F, Ince PG. Patterns and stages of alpha-synucleinopathy: Relevance in a population-based cohort. *Neurology*. 2008; 70:1042–1048. [PubMed: 18362284]

Figure.

An example of an iLBD case with pathology distributed in a pattern consistent with Braak stage 5. LBs are present in neocortical regions, in addition to caudal and rostral brainstem nuclei and mesolimbic cortex. (A) Dorsal motor nucleus of the vagus nerve (B) Substantia nigra (C) Amygdala (D) Frontal cortex (scale bar = 20 μ m).

Table 1

Patterns of α-synuclein pathology in iLBD

	SC	DMN	LC	SN	nbM	Amyg	ERC	CA2/3	Cing	ST	MF
<u>Ascending (N = 11)</u>											
Number:	7/11	9/10	9/11	6/11	1/10	0/10	0/10	0/10	0/11	0/10	0/10
Percent:	64%	90%	82%	55%	10%						
<u>Intermediate (N=10)</u>											
Number:	6/8	6/9	8/10	9/9	8/10	8/9	0/10	1/8	1/10	1/10	1/10
Percent:	75%	67%	80%	100%	80%	89%		12%	10%	10%	10%
<u>Diffuse (N=12)</u>											
Number:	10/11	12/12	12/12	10/10	12/12	12/12	12/12	5/8	9/11	8/12	5/12
Percent:	91%	100%	100%	100%	100%	100%	100%	63%	82%	67%	42%

SC= spinal cord; DMN = dorsal motor nucleus of the vagus; LC= locus ceruleus; SN= substantia nigra; Amyg = amygdala; nbM= nucleus basalis of Meynert; ERC = entorhinal cortex; CA2/3= CA2/3 sector of the hippocampus; Cing = cingulate gyrus; ST = superior temporal gyrus; MF = mid-frontal gyrus

Group demographics and Alzheimer type pathology

Table 2

	Age at death (years)	Braak NFT stage	CERAD SP score	NIA-Reagan	Braak PD stage
<u>Ascending (N = 11; F = 3)</u>					
Range:	63–92	0–IV	0–2	0–2	Stage 1 = 2 Stage 2 = 3 Stage 3 = 6
Median:	76	I	0	0	
<u>Intermediate (N = 10; F = 7)</u>					
Range:	71–94	0–IV	0–3	0–2	Stage 3 = 1 Stage 4 = 9
Median:	83	II	1	1	
<u>Diffuse (N = 12; F = 8)</u>					
Range:	62–103	0–IV	0–3	0–2	Stage 5 = 4 Stage 6 = 8
Median:	84	III	1	1	

N = total number; F = females; NFT= neurofibrillary tangle (0 = no NFT; 1 = transentorhinal; II = entorhinal; III = hippocampus; IV = temporal isocortex; V = frontoparietal isocortex; VI = primary visual cortex); CERAD SP = Consortium to Establish a Registry for Alzheimer Disease senile plaque (0 = no SP; 1 = sparse; 2 = moderate; 3 = frequent); NIA-Reagan = National Institute on Aging-Reagan Institute criteria (0 = not AD, 1 = low likelihood; 2 = intermediate likelihood)