Lewy Body Pathology in Normal Elderly Subjects

William R. Markesbery, MD, Gregory A. Jicha, MD, PhD, Huaichen Liu, MD, and Frederick A. Schmitt, PhD

Abstract

Lewy bodies and Lewy neurites are the hallmark neuropathologic findings in Parkinson disease, Parkinson disease with dementia, dementia with Lewy bodies, and other α-synucleinopathies. They have also been described in the brains of normal older individuals and referred to as incidental Lewy body disease. The purpose of this study was to determine the prevalence of Lewy bodies and Lewy neurites (Lewy body pathology [LBP]) in 139 autopsies from our normal volunteer control group of the University of Kentucky Alzheimer’s Disease Center. All subjects were followed longitudinally and were cognitively normal and without any type of movement disorder, neuropsychiatric features, or other CNS findings. The brains of 33 of 139 normal subjects contained LBP in various regions. The most common regions involved were the medulla (26%), amygdala (24%), pons (20%), and midbrain (20%). No mean statistical differences were found between those with and without LBP on any demographic or cognitive variable, Braak stage, or neurofibrillary tangle and neuritic plaque quantitation. An explanation for the high prevalence of LBP in our elderly, well-educated study group is not clear, although it does not seem to be related to aging or the presence of Alzheimer disease pathology. Overall, our findings support the concept that incidental Lewy body disease most likely represents preclinical or presymptomatic Parkinson disease, Parkinson disease with dementia, or dementia with Lewy bodies.

Key Words: Aging, α-synucleinopathies, Lewy bodies, Lewy neurites.

INTRODUCTION

Lewy bodies (LBs) and Lewy neurites (LNs) are the histopathologic features of Parkinson disease (PD), Parkinson disease with dementia, dementia with Lewy bodies (DLB), and the mixed form of Alzheimer disease (AD) and DLB. They are also found in other neurodegenerative disorders such as progressive supranuclear palsy, corticobasal degeneration, multiple system atrophy, rare cases of neurodegeneration with brain iron accumulation type 1 (Hallervorden-Spatz disease), and several other disease entities (1). In the brainstem, LBs are intracytoplasmic eosinophilic hyaline inclusions with a central core surrounded by a halo-like corona. In the cerebral cortex, LBs do not have a corona; they are sometimes irregular in shape, and some are smaller than those observed in the brainstem. Ultrastructurally, LBs are composed of densely packed filaments associated with dense granular material in the core and radially arranged intermediate filaments in the corona (2, 3). The major component of LBs and LNs is aggregated α-synuclein, which normally functions as a presynaptic protein.

Lewy bodies and LNs have also been described in the brains of normal individuals (4–15); these findings are often referred to as “incidental Lewy body disease” (16). Some of these studies used nonspecific LB markers (4–6) and anticipated the use of α-synuclein immunohistochemistry, a more sensitive and specific method that is currently used to detect Lewy body pathology (LBP). The present study describes LBP in various brain regions in 33 of 139 asymptomatic, cognitively normal, longitudinally followed elderly control subjects.

MATERIALS AND METHODS

Participants

The subjects studied in this report were from the University of Kentucky Alzheimer’s Disease Center normal volunteer control group (17, 18). The present study represents 139 autopsies from 1990 to mid-2008, a period in which we performed 208 autopsies from the normal control group. Excluded from this study were normal subjects who developed DLB, mild cognitive impairment, AD, or other disorders as determined by clinical consensus conference diagnosis and reviewed in a neuropathology consensus conference that combined clinical and neuropathologic findings. Thus, the subjects in this study were cognitively normal elderly without any type of movement disorder, neuropsychiatric features, or other CNS findings. The details of the recruitment and inclusion criteria for the normal control group have been described previously (19). All subjects were contacted at 6-month intervals and had annual detailed cognitive function assessments and neurologic and physical examinations biannually or annually. Since 2000, all subjects underwent annual neurologic and physical examinations, including the Unified Parkinson’s Disease Rating Scale. The details of the annual cognitive assessments of our subjects have been...
described previously (19). Initially, the tests of cognition included the mental status procedures of the Consortium to Establish a Registry for Alzheimer Disease (20), some of the procedures used in the Washington University study of memory and aging project testing battery (21), those used by Eslinger et al (22) supplemented by the Vocabulary and Digit Symbol subtests from the revised Wechsler Intelligence Scale (23) at baseline, and the Trail Making test from the Halstead-Reitan Neuropsychological Test Battery (24). Since 2005, we have used the standard test battery as required by the National Alzheimer’s Coordinating Center for all National Institute on Aging–funded Alzheimer’s Disease Centers that includes most of these measures plus other neuropsychological tests. Neuropsychological data are available at the National Alzheimer’s Coordinating Center in Seattle, WA (www.alz.washington.edu) or by contacting the University of Kentucky Alzheimer’s Disease Center (www.mc.uky.edu/coa). All subjects had normal cognition, intact activities of daily living, and normal neurologic examinations. None carried the diagnosis of PD, Parkinson disease with dementia, preclinical DLB, or other neurologic diseases, and they were not being treated with anti-Parkinson medications.

Tissue Sampling and Processing

The gross neuropathologic evaluation, including surface structures, sections of left hemisphere, and right medial temporal lobe structures, was performed at the time of autopsy. Specimens for biochemical and molecular biologic studies were taken from the left hemisphere along with adjacent sections for histologic evaluations that included 24 different

![FIGURE 1. Lewy body pathology by α-synuclein immunostaining. (A) Moderate (grade 2) Lewy body (LB) and Lewy neurite (LN) formation in the dorsal motor glossopharyngeal/vagal complex of the medulla (40×). Inset: Two LBs (arrows; 200×). (B) Moderate (Grade 2) LBs in the locus ceruleus (arrows; 400×). (C) Moderate (grade 2) LBs (arrows) and LNs in a portion of the substantia nigra (100×). Inset, Higher magnification of LB (500×). (D) Severe (Grade 3) involvement of amygdala with many LBs and LNs (200×). (E) Moderate (Grade 2) LB and LN formation in the nucleus basalis of Meynert (300×). (F) Mild (Grade 1) LB formation in the temporal pole cortex (100×). Magnifications are the original magnifications.](http://jnen.oxfordjournals.org/)

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fibrillary tangles in hippocampal CA1 and subiculum, tions. Gallyas-stained sections were used to quantify neuro-
were quantified in the amygdala, hippocampal CA1 and
parietal lobule, and occipital area 18. Diffuse plaques and NPs
plaque (NPs) were counted in Bielschowsky silver impreg-
nated sections of frontal area 9, middle temporal gyrus, inferior
cingulate gyrus (area 24), and posterior cingulate gyrus (area 23). Specimens were also taken from the hippo-
campus at the level of the lateral geniculate nucleus, entorhinal
cortex, amygdala, ambient gyrus, basal ganglia, nucleus ba-
salis of Meynert, thalamus, midbrain, and cerebellum. Similar
sections were taken from the right hemisphere of most cases
after fixation of the brain, and additional sections were taken
from the cerebellum, midbrain, pons, and medulla. All speci-
mens were processed in the usual manner, and sections were
cut at 8-μm thickness. Sections were stained with hemato-
xylin and eosin and the modified Bielschowsky method. The
Gallyas stain was used for sections of the entorhinal cortex,
hippocampus, and amygdala. All sections of the cortex and
ventromedial temporal lobe structures were stained with 10D-5
(Athena Neurosciences, San Francisco, CA) or the anti-β-
amyloid antibody (Novocastra, Newcastle, UK).

Immunohistochemical staining with the mouse anti–α-
synuclein monoclonal antibody (Novocastra) was used for
assessment of LBs. Immunostaining was performed on
10-μm-thick sections that were pretreated with formic acid,
blocked in 15% filtered horse serum in automation buffer,
incubated with primary antibody for 1 hour, and developed
with the avidin-biotin complex using Nova Red (Vector
Laboratories, Burlingame, CA) as the chromogen.

Neurofibrillary tangles, diffuse plaques, and neuritic
plaques (NPs) were counted in Bielschowsky silver impreg-
nated sections of frontal area 9, middle temporal gyrus, inferior
parietal lobule, and occipital area 18. Diffuse plaques and NPs
were quantified in the amygdala, hippocampal CA1 and
subiculum, and entorhinal cortex in Bielschowsky prepara-
tions. Gallyas-stained sections were used to quantify neuro-
fibrillary tangles in hippocampal CA1 and subiculum,
amygdala, and entorhinal cortex. Senile plaques, diffuse
plaques, and NPs were counted as previously described (25).

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<tr>
<th>Variable</th>
<th>LBP Present</th>
<th>No LBP</th>
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<tr>
<td>Age at death, years</td>
<td>85.58 ± 7.91</td>
<td>83.70 ± 7.87</td>
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<td>Mean education, years</td>
<td>16.06 ± 2.45</td>
<td>16.07 ± 2.41</td>
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<td>Mean time from last evaluation to autopsy, months</td>
<td>8.94 ± 6.12</td>
<td>8.60 ± 6.83</td>
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<tr>
<td>Mean postmortem interval, hours</td>
<td>4.45 ± 4.28</td>
<td>4.95 ± 9.60</td>
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<tr>
<th>Measure</th>
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<tr>
<td>Mini-Mental State Examination</td>
<td>28.13 (2.0)</td>
<td>28.03 (1.5)</td>
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<td>Blessed IMC T errors</td>
<td>2.96 (3.9)</td>
<td>2.36 (2.6)</td>
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<td>Category fluency (animals)</td>
<td>15.48 (5.2)</td>
<td>16.34 (5.8)</td>
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<tr>
<td>15-Item Boston Naming Test</td>
<td>14.24 (1.0)</td>
<td>14.10 (1.4)</td>
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<tr>
<td>Trail Making Test Part A</td>
<td>54.84 (34.9)</td>
<td>54.37 (22.7)</td>
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<tr>
<td>Trail Making Part B</td>
<td>127.14 (55.6)</td>
<td>132.09 (55.8)</td>
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<tr>
<td>Word-list Learning (30 max)</td>
<td>19.87 (4.5)</td>
<td>19.54 (4.3)</td>
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<tr>
<td>Word-list Delayed Recall (10 max)</td>
<td>6.18 (2.2)</td>
<td>6.26 (2.0)</td>
</tr>
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There were no significant differences in any of the Consortium
Establish a Registry for Alzheimer Disease battery of
mental status testing between those with LBP and without
LBP (Table 2). Subjects had been followed for 1 to 15 years
with an average of 7.00 ± 3.88 annual follow-up visits.
The mean time between the last examination and death was
8.60 ± 6.83 months for those without LBP compared with
8.94 ± 6.12 months for those with LBP. The mean age at
autopsy for those without LBP was 83.70 ± 7.87 years
compared with 85.58 ± 7.91 years for those with LBP
(overall mean age, 83.45 ± 7.85 years). The mean years
of education were 16.07 ± 2.40 for non-LBP subjects, whereas
those with LBP had an average of 16.06 ± 2.45 years. All but
2 of the cases were Caucasian. The most frequent causes
of death were myocardial infarcts, pneumonia, congestive heart
failure, chronic obstructive pulmonary disease, and cancer
(none had cerebral metastases).
The fresh brain weights were determined at the time of autopsy. The mean brain weight was 1,216.3 ± 126.9 g for non-LBP subjects and 1,246.4 ± 123.6 g for LBP subjects, which were not statistically different. Because of the cumbersome nature of showing differences between LBs and LNs in each case, they are presented together as LBP in Table 3.

Of the 139 patients studied 33 (23.7%) had LBP in some region of the neocortex, allocortex, brainstem, or olfactory bulb and tract. The most common sites involved were the medulla (26%), amygdala (24%), pons (20%), and midbrain (20%).

In the 8 subjects with LBP limited to the brainstem, 4 cases were limited to the medulla, and all of these were scored as mild; 2 had LBP in medulla, pons, and midbrain; 1 had medullary and pontine LBP only and 1 had midbrain LBP alone; another had medulla, midbrain, and olfactory bulb LBP. Although neuron quantitation was not performed, the substantia nigra did not show meaningful neuron loss in those graded 1+ and 2+, whereas several of those graded 3+ showed mild depigmentation and pigmentary incontinence. One participant had LBP limited to the olfactory bulb only.

The earliest changes in the medulla were limited to the dorsal glossopharyngeal/vagus motor nuclear complex. In more advanced cases, the LBP involved the gigantocellularis reticular nucleus and other reticular nuclei. In the pons, early changes involved the locus ceruleus; in more severely affected cases, there was involvement of the locus ceruleus/subceruleus complex and other neurons of the pontine tegmentum. In the substantia nigra, early changes were in the pigmented neurons of the pars compacta, and with more severe involvement, it was more diffusely scattered in pigmented neurons. There was often mild asymmetry in the LBP between left and right in the brainstem.

The amygdala showed LBP in 24 of 33 cases, but most had only mild involvement. Only 3 cases had LBP only in the amygdala. All but 4 subjects had 2 or more regions of the

<table>
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<th>TABLE 3. Location of LBP in Aged Normal Control Subjects</th>
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<tr>
<td>Sex</td>
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The lack of a rating indicates that there was no LBP in that anatomic structure.

*Time of death unknown.

AC, anterior cingulate; Amy, amygdala; Braak, Staging for neurofibrillary pathology; EC, entorhinal cortex; Fro, frontal; Hippo, hippocampus; IT, inferior temporal; MB, midbrain; Med, medulla; nbM, nucleus basalis of Meynert; OB, olfactory bulb; PMI, postmortem interval; TP, temporal pole.
brainstem involved and had LBP in the amygdala. All cases that contained LBP in the neocortex, allocortex, or nucleus basalis of Meynert had amygdala involvement.

All 6 subjects with neocortical involvement had abundant LBP in medulla, pons, midbrain, and amygdala. Of the 6 subjects with neocortical involvement, 2 met the initial neuropathologic criteria for the diagnosis of DLB (26) or recent refinement of the criteria (27) with LBP in 2 or more cortical areas plus amygdala and entorhinal cortex.

The mean Braak stage for neurofibrillary pathology was 1.80 ± 1.26 in subjects without LBP and 2.09 ± 1.33 with LBP. Frequencies of Braak staging did not differ by groups, \((\kappa^2 = 3.76; p = 0.58)\). No significant differences were found in neurofibrillary tangle and NP counts in all 4 lobes of the neocortex or in hippocampal CA1 and subiculum, entorhinal cortex, and amygdala between those with and without LBP. The 2 groups did not differ in age at autopsy. Lewy body pathology seemed to be more common in the eighth decade.

**DISCUSSION**

To our knowledge, this represents the largest study of LBP in longitudinally evaluated normal control subjects to date. The major finding of the study is that 23% of elderly subjects with normal cognition and no clinical evidence of PD, DLB, or other CNS disorders contained α-synuclein–positive LBP in 1 or more regions of the CNS. Although others have described LBP in normal elderly subjects, none have used longitudinally evaluated elderly normal controls and focused only on LBP in normal aging. In the preimmunocytochemistry era, Lipkin (4) reported LB in 4.9% of control subjects, and Forno (5) found them in 4.7% of routine autopsies. Gibb and Lees (6) found LBP increased from 3.8% to 12.8% between the sixth and ninth decade in 273 patients dying of diseases other than PD. Many of their cases had other neurologic diseases. Since the introduction of α-synuclein immunohistochemistry, Tsuboi et al (7) found LBP in 9.2% of normal elderly subjects, Parkkinen et al found LBP in 11% in 1 study (8) and 13% in another (12), and Wakisaka et al (13) found them in 15%. Jellinger (14) showed that 31% of aged controls had α-synuclein–positive LB in the basal nucleus and in medulla, pons, or midbrain. In a series of 904 autopsied subjects, Parkkinen et al (12) found LBP in the brainstem or basal forebrain nucleus of 106 subjects (13%), but only 32 (30%) did not have any neurologic impairment and were considered normal. In a community-based Japanese population (the Hisayama Study) LBP was present in 15% (11/73) of nondemented subjects without PD (13). Sengoku et al (28) found LBP in 31.9% of consecutive autopsied patients from a general geriatric hospital. In studies of small numbers of longitudinally followed cognitively normal elderly individuals, Knopman et al (11) described LBP in 13% (5/39), and Mikolaenko et al (15) found LBP in 8.3% (3/36).

In a study of 30 incidental LBP cases from 413 autopsies, Del Tredici et al (9) found that LBP begins in the dorsal glossopharyngeal-vagal complex, locus ceruleus/subceruleus complex, caudal raphe nuclei, gigantocellularis reticular nucleus, olfactory bulb, tract and anterior olfactory nucleus but not in the substantia nigra. These subjects were not followed longitudinally but did not have PD, AD, or other neurologic or psychiatric diseases. Of our 7 cases limited to the brainstem, 4 involved medullary nuclei alone, supporting the findings of Del Tredici et al; 9 other cases had only brainstem and amygdala involvement.

It is difficult to compare our results with the other studies because of case selection and study design. As previously noted, only 2 other studies used longitudinally followed systematically evaluated controls (11, 15). Some studies calculated the percentages of α-synuclein–positive normals in all α-synuclein–positive cases rather than the whole autopsy series. Some were designed to compare demented subjects with nondemented controls without regard for movement disorders. Other studies used only specific brain areas rather than a broad spectrum of brain regions. The percentage of normal elderly controls with LBP in the present study (23%) is higher than most others studies except for the reports by Jellinger (14) and Sengoku et al (28).

The reason for the high prevalence of LBP in our study is not clear. Several authors have suggested that aging and severe AD pathology have a major effect in the evolution of LBP (8, 10, 13); 2 of these studies showed an age-related increase in LBP between the eighth and tenth decade (8, 13). Although our subjects with LBP were old (mean age > 80 years), there was no significant difference in mean age of those with and without LBP. In the LBP group, however, the extent of LBP was slightly increased in the eighth and ninth decades compared with the seventh decade.

Our study did not show an association with AD pathology as indicated by statistically insignificant mean Braak scores of 2.1 in subjects with LBP compared with 1.80 in controls without LBP. In addition, NP counts between controls with and without LBP were not significantly different. These results are in agreement with others in which AD pathology does not seem to have a strong effect on the evolution of LBP (13, 14), and LBP and tau or Aβ lesions are not synergistic (15). In addition, the presence of LBP does not indicate a transition to the mixed form of AD/DLB in our study. Those with neocortical and allocortical LBP had Braak stage (i.e. neurofibrillary) scores from 0 to II. None of our LBP subjects showed clinical manifestations of DLB or a decline in cognitive function, even at a late stage of life, suggesting that they were not developing DLB yet. Synergy between AD and DLB pathology may be restricted to subjects who experience progressive clinical symptoms and cognitive decline rather than the asymptomatic, cognitively normal subjects we studied.

Lewy bodies were initially described in the amygdala in AD using α-synuclein immunohistochemistry by Lippa et al (29) and have been reported to occur in this site in 43% to 60% of AD patients (30, 31). The amygdala was also a common site of LBP because it occurred in 24 of our 33 cases with LBP. Interestingly, almost two thirds of those with brainstem LBP also had amygdala involvement. Although LBP was prominent in the amygdala, none had cognitive impairment, which would suggest that LBP in amygdala is not always related to cognitive impairment, as suggested by Parkkinen et al (12).
Jellinger (10) suggested that the burden of α-synuclein pathology was significantly greater in demented patients versus nondemented subjects. Most neuropathologists would agree with that conclusion. Several of our nondemented cases, however, had neocortical and allocortical LBP and met the original neuropathologic criteria for DLB (26). Six of our cognitively normal control subjects had developed Parkinson signs or early neuropsychiatric manifestations of DLB and were excluded from the present study. Each of these cases met the recent neuropathologic criteria for DLB (32) and probably had preclinical or early DLB; the details of these subjects are presented in a separate publication (33).

Braak and Del Tredici (34) developed a staging procedure for LBP associated with PD that begins in the medulla and olfactory structures and continues in a topographic predictable sequence in 6 stages progressively involving olfactory, autonomic, limbic, and somatosensory systems; they suggest that the earliest LBP may develop more or less simultaneously in the medulla and olfactory bulb (Stage 1). Our 1 case with LBP only in the olfactory bulb may represent one in which the change occurred there first, and that this might have been followed by LBP in the medulla if the patient had lived longer. In the cases with brainstem only LBP, 4 had medulla involvement alone, and the pathologic changes were mild and predominantly limited to the dorsal glossopharyngeal/vagal nuclear complex and the nucleus gigantocellularis. One case involved medulla and the locus ceruleus, the former more extensively than the latter. These cases conformed to Braak Stages 1 and 2 (35). Three cases had medulla, locus ceruleus/subceruleus, and substantia nigra LBP and conformed to Braak Stage 3 except that the amygdala was not involved. Eight cases had LBP in the amygdala, medulla, locus ceruleus, and substantia nigra, thereby fulfilling Braak Stage 3 criteria. It would be expected that some of these cases may have clinical findings such as motor symptoms, autonomic, or cognitive decline, but they were not detected. Perhaps, they had subtle undetected clinical findings. Another explanation is that possibly the burden of LBP and neuron loss was not large enough to cause symptoms in some cases or that our cases had strong “brain reserve” to withstand the effects of LBP. Perhaps the high level of education in our subjects (mean, 16 years) plays a role in this regard. Thus, in evaluating elderly, well-educated subjects with no cognitive decline at autopsy, the threshold of LBP causing clinical symptoms may be higher than in the average population.

It is also possible that some of these subjects developed clinical or cognitive changes between the last evaluation and autopsy, although this seems unlikely for most because intervals between the last examination and death of the subjects with LBP (8.94 ± 6.12 months) were relatively short. A more likely explanation for our findings is based on the recognition that diseases such as PD, AD, and DLB have pathologic manifestations long before the classic clinical manifestations appear. In some PD cases, autonomic, olfactory, and sleep disorders antedate motor symptoms and signs by many years (36–38). Del Tredici et al (9) and others (6, 39) suggest that LBP in the brainstem represents the precursor of PD. It is unlikely that our findings represent nonspecific alterations found in the aging brain. DelleDonne et al (16) showed that subjects with incidental Lewy body disease had diminished immunoreactivity for tyrosine hydroxylase and vesicular monoamine transporter 2 in the putamen compared with normal controls; the decline in dopaminergic immunoreactivity correlated inversely with substantia nigra neuron loss and PD stages. Their findings suggest that incidental Lewy body disease most likely represents preclinical PD. It is possible that most, if not all, of our subjects were in the presymptomatic phase of PD. Parkinson disease with dementia, or DLB and, if they had lived longer, would have demonstrated neurologic impairment. Our study also suggests that a large number of normal elderly are probably at risk for developing these disorders.

ACKNOWLEDGMENTS

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REFERENCES

1. Giasson BI, Lee VM, Trojanowski JQ. Parkinson’s disease, dementia with Lewy bodies, multiple system atrophy and the spectrum of diseases
34. Braak H, Del Tredici K. Neuroanatomy and Pathology of Sporadic Parkinson’s Disease. Berlin, Germany: Springer-Verlag, 2009