Lewy Body Pathology in Familial Alzheimer Disease

Evidence for Disease- and Mutation-Specific Pathologic Phenotype

James B. Leverenz, MD; Mark A. Fishel, MD; Elaine R. Peskind, MD; Thomas J. Montine, MD, PhD; David Nochlin, MD; Ellen Steinbart, RN, MA; Murray A. Raskind, MD; Gerard D. Schellenberg, PhD; Thomas D. Bird, MD; Debby Tsuang, MD, MS

Background: The origin and significance of Lewy bodies and neurites (Lewy body pathology [LBP]) in Alzheimer disease (AD) are poorly understood.

Objective: To examine LBP in the brainstem, limbic cortex, and neocortex of a large number of familial AD cases with mutations in 2 presenilin (PSEN) genes.

Methods: Twenty-five familial AD cases with 9 known PSEN 1 mutations and 14 familial AD cases with a single PSEN 2 mutation (N141I) were examined for LBP using α-synuclein immunohistochemistry and sampling of multiple brainstem and cortical regions.

Results: The amygdala was the most vulnerable site for LBP. In fact, virtually all (24 [96%] of 25 cases) of the PSEN 1 mutation cases had LBP in the amygdala. The PSEN 1 mutation cases also had more frequent LBP in the amygdala and neocortex than those with the PSEN 2 mutation. However, within families with a single mutation of either PSEN 1 or PSEN 2, there was frequent variability of the LBP.

Conclusion: These findings suggest that there are genetic influences on the presence of LBP in familial AD as demonstrated by the differences between PSEN 1 and PSEN 2 mutation cases.

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with genetic mutations associated with familial AD (FAD). Previous investigators have described the frequency of LBP in AD associated with presenilin 1 (PSEN 1), presenilin 2 (PSEN 2), and amyloid precursor protein (APP) gene mutations and in Down syndrome. These studies found a high frequency of LBP (50%-60%) in these FAD groups. To date, no studies to our knowledge have investigated risk factors or full anatomical distribution for LBP within these subgroups of FAD. Substantial clinical and pathologic heterogeneity in the presence and distribution of LBP in families with apparent autosomal dominant dementia with LBs has been previously described. Investigation of LBP in families with a known single mutation for AD (therefore the same genetic cause) will also allow us to test the hypothesis that concomitant LBP is heritable within families.

The current study examines LBP within families with known PSEN 1 or PSEN 2 mutations. In this study, we will extend previous findings in FAD by examining the presence of LBP in the following: (1) a larger number of cases, (2) families with a single PSEN 2 mutation, (3) individual families with multiple autopsies available for neuropathological examination, and (4) multiple anatomical regions, including the medulla, amygdala, and neocortex.

METHODS

SAMPLES

Twenty-five FAD cases with known PSEN 1 mutations were available for neuropathological examination. Clinical and demographic characteristics of these individuals are outlined in Table 1. Nine different PSEN 1 mutations have been found in these families (Table 2). Among these 9 families, 4 had 1 affected individual (mutations H163R, I143T, L418F, and M146L). 2 had 2 affected individuals (mutations A431E and M233L). 1 had 3 affected individuals (mutation E120D) and 2 had 7 affected individuals (mutations A260V and G209V) with tissue available for analysis. Clinical and neuropathological characteristics in some of these families have previously been described.

Sixteen cases from 8 families with FAD and a single founder mutation (N141I) in the PSEN 2 gene were available for neuropathological examination. Fourteen of these cases had a clinical history of dementia. These families have previously been described in detail and are of Volga German ancestry. Of note, 6 members from 1 family had autopsy material available for evaluation (family 1, Table 2), including 2 unaffected individuals without a clinical history of dementia or a PSEN 2 mutation (not included in Table 2). Summary clinical and demographic characteristics of these individuals are outlined in Table 1 (excluding the 2 individuals without dementia).

Table 1. Demographics of PSEN 1 and PSEN 2 Mutation-Associated Familial Alzheimer Disease

<table>
<thead>
<tr>
<th>Mutation</th>
<th>PSEN 1, Mean ± SD (n)</th>
<th>PSEN 2, Mean ± SD (n)</th>
<th>P Value</th>
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<tr>
<td>Age at onset</td>
<td>42.13 ± 7.08 (24)</td>
<td>57.00 ± 8.86 (14)</td>
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<tr>
<td>Age at death</td>
<td>51.60 ± 8.90 (25)</td>
<td>68.57 ± 9.83 (14)</td>
<td>&lt;.01</td>
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<tr>
<td>Duration</td>
<td>9.83 ± 5.11 (24)</td>
<td>11.00 ± 5.22 (14)</td>
<td>.51</td>
</tr>
<tr>
<td>Braak stage</td>
<td>5.48 ± 0.51 (25)</td>
<td>5.14 ± 0.77 (14)</td>
<td>.10</td>
</tr>
<tr>
<td>Male (16)</td>
<td>(7)</td>
<td>.73†</td>
<td></td>
</tr>
<tr>
<td>Female (9)</td>
<td>(7)</td>
<td>(7)</td>
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*Unpaired t test unless otherwise specified.
†The χ² test was applied to the male-female ratio.

Table 2. Clinical and Neuropathological Characteristics of PSEN 1 Mutation Cases

<table>
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<tr>
<th>Mutation</th>
<th>Age at Onset, y</th>
<th>Age at Death, y</th>
<th>Duration, y</th>
<th>Sex</th>
<th>APOE Genotype</th>
<th>Braak Stage</th>
<th>Amygdala (SNCA)</th>
<th>Cingulate Gyrus (SNCA)</th>
<th>Neocortex (SNCA)</th>
<th>Substantia Nigra (H&amp;E)</th>
<th>Substantia Nigra (SNCA)</th>
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Abbreviations: APOE, apolipoprotein E; H&E, hematoxylin-eosin; NA, not available; SNCA, α-synuclein; +, presence; −, absence.
*Neurites only.
NEUROPATHOLOGICAL EVALUATION

Neuropathological evaluation was performed at the University of Washington Medical Center, Seattle, by neuropathologists from the Department of Pathology and the Alzheimer Disease Research Center. Neuropathological examinations focused on the cingulate gyrus, superior and middle frontal gyri, medial orbital cortex, superior, middle, and inferior temporal gyri, inferior parietal lobule, medial occipital cortex, hippocampus, amygdala, parahippocampal gyrus, hypothalamus, mamillary bodies, thalamus, midbrain,pons, medulla, and cerebellum. Standard tissue staining consisted of hematoxylin-eosin, thioflavin-S, and the modified Bielschowsky silver method on 8-μm paraffin-embedded sections. Braak staging was based on evaluation of sections stained by a modified Bielschowsky stain.

SNCA IMMUNOSTAINING

Immunohistochemical staining was performed with a well-characterized monoclonal antibody to SNCA (LB 509; Zymed, San Francisco, Calif) in the frontal cortex, cingulate gyrus, amygdala, hippocampus, substantia nigra, locus coeruleus, and medulla.23 Substantia nigra slides were pretreated with hydrogen peroxide to depigment neuromelanin and to allow for better visualization of immunopositive inclusions.25 A case of dementia with LBs was used as a positive control with all of the immunostaining. Elimination of the primary antibody was used as a negative control. For confirmation of immunonegative or mild LB 509 immunostaining positive staining, we used a second antibody to SNCA (Syn 303; titer, 1:1000; generous gift from John Q. Trojanowski, MD, PhD, University of Pennsylvania, Philadelphia). The methods, in brief, included deparaffinization of 10-μm sections from paraffin blocks in xylene and then hydration through graded alcohols to distilled water. Sections were then pretreated with 88% formic acid for 5 minutes, rinsed in phosphate-buffered saline, and then treated with 3% hydrogen peroxide. After a 60-minute block in 5% milk, sections were incubated at room temperature with primary antibody (LB 509 at titers of 1:50-1:400, Syn 303 at a titer of 1:1000) for 1 hour. After the phosphate-buffered saline rinse, the sections were then incubated with secondary antibody for 45 minutes. After an additional phosphate-buffered saline rinse, the sections were incubated in an avidin-biotin complex for 1 hour. Sections were incubated in diaminobenzidine for 10 minutes, rinsed, dipped in lithium carbonate solution, rinsed with tap water, dehydrated through graded alcohols, and cleared in xylene.

ASSESSMENT OF SNCA IMMUNOSTAINING

All of the available slides were assessed for the presence or absence of SNCA immunopositive intraneuronal, cytoplasmic inclusions and extraneuronal neurites. In the brainstem (substantia nigra, locus coeruleus, medulla), LB pathology was assessed in either single sections with bilateral substantia nigra, locus coeruleus, and medulla or in 2 unilateral sections from these regions. Above the tentorium, single sections from the following regions were assessed: amygdala, hippocampus (level of the lateral geniculate), cingulate gyrus (level of the nucleus accumbens), and neocortex (frontal, parietal, or occipital).

APOLIPOPROTEIN E GENOTYPING

The apolipoprotein E genotype was obtained from blood samples. The genotyping was performed using the dot-blot method and replicated using a restriction enzyme digest method.35,36 The two methods yielded the same apolipoprotein E genotype in all of the cases.

RESULTS

SNCA PATHOLOGY IN PSEN 1 MUTATION-ASSOCIATED AD

Twenty-four (96%) of the 25 PSEN 1 mutation-associated FAD cases had LBP using SNCA immunohistochemistry in at least 1 brain region (Table 2). Twenty-three (96%) of 24 PSEN 1 mutation-associated FAD cases with amygdala available had SNCA pathologic change. Twenty-two of these amygdala-positive cases had both SNCA immunopositive neuronal inclusions and neuritic changes whereas 1 case had only neuritic LBP in the amygdala (confirmed with both LB 509 and Syn 303 immunostaining). Regional LBP varied between and within families and is outlined in Table 2. Notably, in patients with the PSEN 1 A260V mutation, 5 (83%) of 6 cases had diffuse LBP with SNCA pathologic change extending to the neocortex. In contrast, in individuals with a G209V mutation, only 2 (29%) of 7 had neocortical LBP. The difference in positive neocortical LBP between these 2 mutations approached statistical significance (P = .08, Fisher exact test). Variability in anatomical LBP distribution also occurred within families with the same PSEN 1 mutation (Table 2), although all but 1 PSEN 1 mutation case had LBP. Comparisons of PSEN 1 mutation cases with no or restricted LBP (amygdala involvement only) vs those with more diffuse LBP (limbic, neocortical, or brainstem involvement) revealed that cases with more diffuse LBP had a significantly longer duration of illness (mean ± SD duration, 12.17 ± 5.86 years vs 7.50 ± 2.88 years, respectively; P = .05, t test). However, there was no significant difference for age at onset or Braak stage between PSEN 1 mutation cases with no or restricted LBP and those with more diffuse LBP (mean ± SD age at onset, 42.86 ± 6.83 years vs 43.10 ± 6.67 years, respectively, and mean ± SD Braak stage, 5.33 ± 0.58 vs 5.50 ± 0.69, respectively; both P ≥ .05, t test).

SNCA PATHOLOGY IN PSEN 2 MUTATION-ASSOCIATED AD

Nine (64%) of 14 PSEN 2 mutation-associated FAD cases had LBP (Table 3). Lewy body pathology was less frequent outside of the amygdala, especially in the neocortex, where only 1 (18%) of 12 cases demonstrated SNCA pathologic change. For the 14 PSEN 2 mutation-associated FAD cases, there was no difference in age at onset, duration of dementia, or Braak stage between those with and without any LBP (P = .05, t test). Specifically, although the duration of illness was longer in PSEN 2 FAD cases with LBP than in those cases without LBP, this did not reach statistical significance (mean ± SD duration, 12.71 ± 5.79 years vs 9.29 ± 4.31 years; respectively; P = .23, t test).

Of special interest, 1 previously described PSEN 2 mutation case37 with limited neurofibrillary tangle pathologic abnormalities (Braak stage III) and severe amyloid angiopathy had SNCA immunopositive inclusions and neurites in the amygdala (family 1, age at onset, 73 years, Table 3).

Finally, in the 2 family members without clinical dementia and without a PSEN 2 mutation, there were no
significant AD pathologic changes or any evidence of LBP (data not shown).

**COMPARISON OF SNCA PATHOLOGY IN PSEN 1 AND PSEN 2 MUTATION-ASSOCIATED AD**

The SNCA immunopositive cases were significantly more frequent in PSEN 1 mutation-associated FAD than in PSEN 2 mutation cases (24 [96%] of 25 cases vs 9 [64%] of 14 cases, respectively; \( P \leq .05 \), Fisher exact test) (Figure). In addition, LBP in the neocortex was significantly more frequent in the PSEN 1 mutation FAD cases than in the PSEN 2 mutation cases (10 [42%] of 24 cases vs 1 [9%] of 12 cases, respectively; \( P = .05 \), Fisher exact test). There was also a higher frequency of LBP in the cingulate gyrus of PSEN 1 mutation cases vs the PSEN 2 cases (12 [59%] of 22 cases vs 3 [23%] of 12 cases, respectively; \( P = .10 \), Fisher exact test), but this did not reach statistical significance. Interestingly, the frequency of LBP in the brainstem was virtually identical for PSEN 1 and PSEN 2 mutation cases.

**APOLIPOPROTEIN E GENOTYPE**

Among those individuals with a PSEN 1 mutation, there were 18 with the APOE*3/*3 genotype, 3 with the APOE*2/*3 genotype, and 2 with the APOE*3/*4 genotype (Table 2). For those individuals with a PSEN 2 mutation, there were 8 with the APOE*3/*3 genotype, 3 with the APOE*2/*3 genotype, and 2 with the APOE*2/*4 genotype (Table 3). There was no clear relationship between the presence of an APOE*4 allele and the presence or severity of LBP; however, there were only 5 cases that carried this allele.

**COMMENT**

Our findings suggest that the frequency and extent of LBP in FAD may depend, at least in part, on the causative PSEN mutation and gene. We found that 24 (96%) of 25 PSEN 1 mutation-associated FAD cases had LBP compared with 9 (64%) of 14 PSEN 2 cases. The high frequency of LBP in PSEN 1 mutation-associated FAD also appears to be greater than reported in sporadic AD and Down syndrome.\(^9,23\) In addition, in our sample, PSEN 1 mutation-associated dementia cases were also significantly more likely than PSEN 2 mutation cases to have neocortical LBP.

Variability in the presence and extent of LBP was observed between and within families for both PSEN 1 and PSEN 2 mutation-associated FAD. In FAD cases with a PSEN 1 mutation, more diffuse LBP appeared to be associated with the A260V mutation whereas other PSEN 1 mutations (eg, G209V) had LBP frequently restricted to the amygdala. Despite having the same mutation, PSEN 2 mutation-associated FAD cases also showed variability for the presence and anatomical extent of LBP (families 1 and 2, Table 3).

Several previous studies have examined the frequency and distribution of LBP in both sporadic AD and FAD using SNCA immunostaining. Hamilton\(^5\) exam-
ined a large sample of sporadic AD (nonfamilial cases from an AD research center) and found SNCA pathologic change in 57% of the cases, with the most frequent LBP being found in the amygdala. Lippa et al\(^7\) found a similar frequency (65%) of LBP in cases of PSEN 1 mutation-associated FAD using detection methods almost identical to those used by both Hamilton\(^2\) and the current study. In contrast, using different SNCA antibodies, other groups have reported somewhat lower frequency of LBP in AD (32%-52%)\(^{3,9}\). The lower frequency of LBP in AD observed by these latter groups is likely owing, at least in part, to differences in methods (eg, the use of different SNCA antibodies with different sensitivities to the detection of LBP). In addition, and consistent with our results, differences between AD samples (eg, FAD vs sporadic AD or PSEN 1 vs PSEN 2 mutation-associated AD) will likely also influence the frequency of observed LBP.

Our finding that virtually all of the PSEN 1 mutation cases had LBP would appear to contradict findings described by Lippa et al.\(^7\). However, a closer examination of the PSEN 1 families from the study by Lippa and colleagues reveals that the lower frequency of LBP is primarily owing to cases with the A246E mutation in PSEN 1. Only 1 (14%) of 7 cases with this mutation had LBP whereas the remaining PSEN 1 mutation cases had a very high frequency of LBP (10 [91%] of 11 cases). Exclusion of the cases with the A246E mutation reveals findings that are quite similar to those described in this study. This also would appear to support our contention that there can be a mutation-specific influence on coexistent LBP in PSEN 1 mutation-associated FAD. Similarly, individuals with different APP mutations have also demonstrated variability in the presence of LBP.\(^{22}\) Again, these findings suggest that there are mutation-specific effects on the development of LBP. Finally, given that some subtypes of FAD have LBP in virtually all of the cases, these findings suggest that LBP can be pathophysiologically linked to AD and is not just a coincident disease process.

To our knowledge, this is the first study to examine the anatomical distribution of LBP throughout the brainstem, limbic cortex, and cerebral cortex of FAD with a PSEN 2 mutation. Lippa et al\(^7\) had previously reported a very low frequency of LBP (1 [14%] of 7 cases) in PSEN 2 mutation cases. However, the previous study was limited by the availability of tissue from multiple anatomical regions (only 1 case had the amygdala available for analysis), and there was no assessment of lower brainstem LBP. Our findings in the neocortex of PSEN 2 cases were similar to those by Lippa and colleagues, as we found limited LBP (note that there were 4 shared cases between our studies). However, we were able to extend their previous findings by studying LBP in the amygdala and brainstem. We found a much higher frequency of LBP in PSEN 2 mutation cases than previously reported (7 [64%] of 11 cases), primarily owing to pathologic changes in the amygdala. Since all of the PSEN 2 cases had the same mutation, differences in clinical or other pathologic risk factors likely exist to account for the variability in LBP.

The finding that LBP was restricted to the amygdala in 1 PSEN 2 mutation case with modest AD pathologic change, Braak stage III, would also suggest that the severity of AD pathologic change is not the only risk factor for coexistent LBP. As yet, unidentified regional pathologic abnormalities and genetic and environmental risk factors likely contribute to the development of LBP in PSEN 2 mutation-associated FAD.

It is not fully apparent why PSEN 1 mutation-associated FAD has more frequent and diffuse LBP than PSEN 2 mutation-associated FAD. It could be argued that PSEN 1 mutation-associated FAD is a more aggressive form of AD with an earlier age at onset. In fact, most articles\(^{40,41}\) suggest that PSEN 1 mutation-associated FAD has greater β-amyloid peptide deposition in the brain than sporadic AD, especially β-amyloid peptide 42/43. One study has also described more severe β-amyloid peptide deposition in PSEN 1 vs PSEN 2 mutation-associated FAD\(^3\), although this finding has not been confirmed.\(^{42}\) Also of interest, the 1 PSEN 1 mutation associated with infrequent LBP (A246E)\(^7\) is also described to have a relatively later age at dementia onset (mean age at onset, 53 years) for PSEN 1 mutation-associated FAD.\(^{44}\) Using a semiquantitative assessment of AD pathologic change,\(^{3,44}\) we did not find a relationship between the severity of AD pathologic change and the presence of LBP in either of the FAD groups, and PSEN 1 and PSEN 2 mutation-associated FAD had a similar duration of illness in our sample. However, these semiquantitative measures may not be adequately sensitive to pick up differences in the density of AD pathologic changes. In our sample, PSEN 1 mutation cases with more anatomically diffuse LBP had a longer duration of illness (vs PSEN 1 mutation cases with LBP limited to the limbic areas). The duration of illness was also greater in PSEN 2 mutation cases with any LBP, but the difference was not statistically significant. Although the origin of LBP in FAD remains unclear, some evidence suggests that aggressiveness and duration of the disease may contribute to the occurrence of this additional pathologic abnormality in FAD.

Two recent articles\(^{21,22}\) have addressed the distribution of LBP in dementia and PD. Marui et al\(^21\) examined LBP in 27 cases of dementia with LBs and proposed a 4-stage process beginning in the limbic cortex (specifically the amygdala) and progressing to involvement of cortical regions. They did not describe brainstem LBP in their study. Braak et al\(^22\) examined LBP in elderly persons with PD and normal elderly persons, and they proposed that this pathologic abnormality initially begins in the medulla and olfactory bulb and progresses rostrally through the brainstem and subsequently into the limbic cortex and neocortex. Our findings are consistent with the proposed staging of dementia with LBs by Marui and colleagues. In the current study, cases of PSEN 1 and PSEN 2 mutation-associated FAD with the least severe LBP showed this pathologic abnormality only in the amygdala. Brainstem and cortical LBPs were observed only in cases that also had amygdala involvement. Braak and colleagues also suggested that the anatomical progression of LBP may be different in cases with dementia. These findings raise the possibility that in PD and dementia with LBs, there is a different anatomical distribution of LBP. In future neuropathologically based studies of LBP-associated diseases, it will be important to characterize the anatomical distribution of this pathologic abnormality. This distinction could impact classification of LBP disorders for future clinicopathologic correlations as well as epidemiologic and genetic studies.
Coexistent LBP in AD has been associated with unique clinical features, including neuropsychological profile, response to therapy, and rate of progression. The FAD cases included in this study were recruited from multiple North American locations. In many circumstances, detailed clinical evaluations were unavailable. Thus, we were unable to examine other clinical characteristics (eg, parkinsonism and hallucinations) frequently associated with LBP.

In conclusion, our findings suggest that LBP is a very frequent coexistent pathologic abnormality in FAD. In addition, specific genetic mutations may influence the presence and extent of LBP. In these FAD cases, the first frequent coexistent pathologic abnormality in FAD is subsequently associated with LBP. In contrast to PD where the first LBP may occur in the medulla, future studies that investigate the impact of other genetic differences predisposing to the development of LBP in both FAD and sporadic AD will lead to a better understanding of this important pathologic change in AD.

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Correspondence: James B. Leverenz, MD, Veterans Affairs Puget Sound Health Care System (116MIRECC), 1660 S Columbian Way, Seattle, WA 98108 (leverenz@u.washington.edu).

Author Contributions: Study concept and design: Leverenz, Peskind, Raskind, and Tsuang. Acquisition of data: Leverenz, Fishel, Peskind, Montine, Noclin, Steinbart, Raskind, Schellenberg, Bird, and Tsuang. Analysis and interpretation of data: Leverenz, Raskind, Schellenberg, and Tsuang. Drafting of the manuscript: Leverenz, Fishel, Montine, Steinbart, and Tsuang. Critical revision of the manuscript for important intellectual content: Leverenz, Peskind, Noclin, Raskind, Schellenberg, Bird, and Tsuang. Statistical analysis: Tsuang. Obtained funding: Leverenz, Peskind, Raskind, and Schellenberg. Administrative, technical, and material support: Leverenz, Peskind, Montine, Steinbart, Raskind, Schellenberg, Bird, and Tsuang. Study supervision: Leverenz and Schellenberg.

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**Announcement**

**Calendar of Events: A New Web Feature**

On the new Calendar of Events site, available at [http://pubs.ama-assn.org/cgi/calendarcontent](http://pubs.ama-assn.org/cgi/calendarcontent) and linked off the home page of the Archives of Neurology, individuals can now submit meetings to be listed. Just go to [http://pubs.ama-assn.org/cgi/cal-submit/](http://pubs.ama-assn.org/cgi/cal-submit/) (also linked off the Calendar of Events home page). The meetings are reviewed internally for suitability prior to posting. This feature also includes a search function that allows searching by journal as well as by date and/or location. Meetings that have already taken place are removed automatically.