Relation of Quantitative Indexes of Concurrent α-Synuclein Abnormalities to Clinical Outcome in Autopsy-Proven Alzheimer Disease

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Background: Lewy bodies (LBs) and Lewy neurites are frequent concomitant neuropathologic observations in clinical and neuropathologically defined Alzheimer disease (AD), but their relation to clinical features in AD is uncertain. Most studies used semiquantitative measures to determine the presence or absence of LB abnormalities.

Objective: To determine the clinical consequences of LB abnormalities in the setting of AD.

Design: Prospective study.

Setting: Three outpatient research and treatment centers.

Participants: Fourteen autopsy cases with a pathologic diagnosis of AD abnormalities and concomitant LBs followed semiannually for up to 8 years (mean age at intake, 72 years; mean age at death, 77 years; mean education, 15 years; 12 women).

Main Outcome Measures: The modified Mini-Mental State Examination was used to assess cognitive function. The Unified Parkinson Disease Rating Scale was used to rate extrapyramidal motor signs. Hallucinations were evaluated using the Columbia University Scale for Psychopathology in Alzheimer's Disease. Time from the first evaluation in which diagnostic criteria for probable AD were met to death was used to determine illness duration. Quantitative measures of LB abnormalities were obtained for the frontal cortex, entorhinal cortex, substantia nigra, and hippocampus.

Results: Independent-samples *t* tests were used to assess whether the degree of LB abnormality varied as a function of the presence or absence of hallucinations and extrapyramidal signs. Pearson *r* correlations were run to examine whether there was a relation among LB abnormalities, cognitive function, and illness duration. There was no relation between quantitative neuropathologic indexes of LB abnormalities and clinical outcome.

Conclusion: The variability of clinical features in AD was not related to the presence or degree of LB abnormalities.

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CURRENT CONSENSUS GUIDELINES[1] for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB) represent an attempt to synthesize previous studies of dementia associated with LB abnormalities and to develop uniform diagnostic criteria. These guidelines may be relevant to the diagnosis of Alzheimer disease (AD) given that one third to one half of patients with AD have concomitant LB abnormalities when examined at autopsy.[2] Previous studies[3-17] produced mixed results when examining the relation of LB abnormalities to clinical features such as extrapyramidal signs (EPSs), psychiatric features, changes in cognitive status, and changes in the course or progression of dementia in patients with confirmed AD.

Stern et al[2] reported that LB abnormalities were not related to distinct clinical features in 51 autopsy cases with confirmed AD from the Predictors Study cohort.[18,19] However, the negative findings might have been due to limitations of the semiquantitative rating method used to determine the presence or absence of LB abnormalities.

The goal of the present study is to extend the previous observations by studying additional brain areas and types of pathologic lesions. The frontal and entorhinal cortices, the hippocampus, and the substantia nigra were examined for LBs and Lewy neurites. Moreover, we used immunostaining to identify these lesions, systematic random sampling to provide quantitative estimates of LB and Lewy neurite numbers, and image analysis approaches to assess amyloid burden, neurofibrillary tangle number, and neuropil thread number. This allowed us to examine the relation of the pathologic lesions to clinical symptoms and to one another.

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METHODS

PARTICIPANTS

The Predictors Study consists of 236 patients with probable AD[20,21] who were recruited and studied at 3 sites: 91 patients at Columbia Medical Center, 84 at Johns Hopkins School of Medicine, and 61 at Massachusetts General Hospital. The inclusion and exclusion criteria and evaluation procedures of the Predictors Study have been fully described elsewhere.[18,19] At entry into the study, patients were required to have mild-to-moderate dementia, which was operationalized as a modified Mini-Mental State Examination (mMMSE) score of 30 or greater (equivalent to ≥16 on the Folstein MMSE). Patients were evaluated every 6 months.

Fourteen autopsy cases with adequate blocks for detailed quantitative neuropathologic analysis of LB abnormalities are reported herein. All the participants had cortical neurofibrillary tangles and were Braak stage V or VI; 12 were women and 2 were men. Mean±SD age at intake was 72±6.6 years and at death was 77±7.7 years. Mean±SD education was 15±2.4 years. Mean±SD mMMSE score at entry was 37±7.2, indicating a relatively mild level of dementia. Mean±SD mMMSE score at the last evaluation was 10.71±10.0. Of the 14 participants, 7 had hallucinations and 10 had EPSs. Mean±SD illness duration was 10.07±3.91 years. The median±SD time from the last evaluation to death was 0.61±0.55 year.

MEASURES

Cognition

Cognition was assessed using the mMMSE.[22] Modifications to the original MMSE include the addition of digit span forward and backward,[23] 2 additional calculation items, recall of the current and 4 previous presidents of the United States, confrontation naming of 10 items from the Boston Naming Test,[24] 1 additional sentence to repeat, and 1 additional figure to copy. The mMMSE has a maximum of 57 points, with lower scores indicating poorer cognitive function.

Extrapyramidal Signs

Selected items from the Unified Parkinson Disease Rating Scale[25] were used to rate EPSs. Hypophonia, masked facies, resting tremor, rigidity (neck and each limb), bradykinesia and hypokinesia, and posture and gait abnormalities were rated as absent, slight, mild-moderate, marked, or severe.[26] In addition to evaluating individual motor signs, the presence or absence of EPSs in general was considered. Patients who had at least 1 sign rated mild-moderate or worse were considered to have EPSs because ratings of this severity are relatively more reliable and are likely to be noted by most clinicians.[26] Our analysis included drug-induced and non–drug-induced EPSs. If, at the visit when EPSs were first detected, the patient was currently taking or had ever taken medications that could induce EPSs, then they were considered to be drug induced; otherwise they were considered to be non–drug induced, even if at subsequent visits the patient received medications that could induce EPSs.

Psychiatric Symptoms

Hallucinations were evaluated using the Columbia University Scale for Psychopathology in Alzheimer's Disease,[27] a short, semistructured rating scale that can be administered by clinicians or research technicians. The frame of inquiry is the month before examination.[27] Interrater reliability for the major symptom categories was established for concurrent rating of a single interview (κ=0.74-1.00) and for separate interviews (κ=0.53-0.73). The presence or absence of hallucinations at any time during follow-up was used for the present study.

Illness Duration

The time elapsed from the first evaluation in which diagnostic criteria for probable AD were met until death was used to determine the illness duration.

NEUROPATHOLOGIC EVALUATION

Neuropathologic assessments were performed on the substantia nigra, entorhinal cortex, hippocampus, and frontal cortex to survey brainstem, limbic and paralimbic, and neocortical regions with a wide range of susceptibility to LBs, neurofibrillary tangles, and amyloid deposition.[8,28] We selected brain regions representative of lower (hippocampus and frontal cortex), intermediate (entorhinal cortex), and high (substantia nigra) densities of LBs based on studies of Parkinson disease and DLB.[3,8] The availability of pathologic tissue specimens was also considered in selecting the target regions.

Evaluation of LBs

Quantitative neuropathologic studies were conducted in paraffin-embedded sections, 12-μm thick, from the entorhinal cortex, substantia nigra, frontal cortex (middle frontal gyrus), and hippocampus. Sections were stained with antibodies against α-synuclein, which is recognized as a specific immunostain for LB abnormalities.[29,30] The LB abnormalities count was performed on adjacent sections for α-synuclein using an objective lens (magnification ×40) and scanning the whole cortex available for each slide. The total number per volume obtained with each immunostain was compared to further characterize the use of α-synuclein in recognizing LBs. The data were recorded using an image analysis system (Bioquant Image Analysis Corp, Nashville, Tenn). This program provides stereologic overlays to assist in estimating the total number of LBs in cortical areas and records the different positions of each of the counted structures using x and y coordinates.

Evaluation of Lewy Neurites

We examined ubiquitin-immunoreactive neuritic degeneration, which is now accepted as a distinctive part of LB abnormality in patients with DLB. These lesions are preferentially present in the CA2 and CA3 regions of the hippocampus, and their extent usually correlates with the density of cortical LBs. These neurites were studied using α-synuclein immunostains. An estimate of the total length of abnormal neurites was derived using the stereologic fractionater procedure. Briefly, a "probe" (a special grid that is anisotopic with respect to the boundaries of the field) was overlaid on the video image, and the number of times a neurite crossed a grid line was recorded using the exclusion lines and the top and bottom exclusion planes of the optical disector approach. This number is proportional to the total length of neuritic staining present in a field.

Evaluation of Amyloid Burden, Neuropil Threads, and Neurofibrillary Tangles

Sections were stained for β-amyloid peptide using the antibody 10D5 (Elan Corp, Dublin, Ireland) with diaminobenzidine visu-

Table 1. Relation of Lewy Body and Lewy Neurite Abnormalities to Hallucination and Extrapyramidal Sign Status

	t Test	*df*	*P* Value
Hallucinations			
Lewy body abnormalities			
Frontal cortex	–0.81	11	.43
Entorhinal cortex	–0.17	11	.87
Substantia nigra	–0.50	12	.63
Hippocampus	0.21	12	.84
Lewy neurite abnormalities			
Frontal cortex	0.04	11	.97
Entorhinal cortex	–0.45	11	.66
Substantia nigra	0.06	12	.96
Hippocampus	0.86	12	.41
Extrapyramidal Signs			
Lewy body abnormalities			
Frontal cortex	0.42	11	.69
Entorhinal cortex	1.31	11	.22
Substantia nigra	–0.68	12	.51
Hippocampus	0.60	12	.56
Lewy neurite abnormalities			
Frontal cortex	–0.08	11	.94
Entorhinal cortex	0.25	11	.81
Substantia nigra	–1.72	12	.11
Hippocampus	1.19	12	.26

alization.[31] The percentage of cortex covered by senile plaques was assessed in a region 700 µm wide × the depth of the cortex. Neuropil threads were assessed using AT8 anti–paired helical filament tau immunostaining and a probe overlaid on the videotape display analogous to that described for Lewy neurite assessments. Neurofibrillary tangles stained with AT8 anti–phospho-tau were counted in a 700-µm-wide region of full cortical thickness using the optical disector technique.[31,32]

RESULTS

We used *t* tests for independent samples to assess whether the degree of LB and Lewy neurite abnormalities in each of the 4 locations varied as a function of the presence or absence of hallucinations and EPSs (**Table 1**). There was no difference in the extent of these pathologic features as a function of hallucinations or EPS status. Although not significant, LB abnormalities in the entorhinal cortex and Lewy neurites in the substantia nigra were greater in individuals with EPSs.

Pearson *r* correlations were calculated to examine whether there was a relation between LB and Lewy neurite abnormalities and 3 continuous measures: mMMSE score from the last examination, rate of cognitive decline (operationalized as the difference between the first and last mMMSE scores), and illness duration (**Table 2**). There were no significant relationships between LB or Lewy neurite abnormalities and any of the 3 clinical features. Although not significant, Lewy neurites in the entorhinal cortex and substantia nigra tended to be inversely related to cognitive status.

We also considered that the relation of LB or Lewy neurite abnormalities and clinical features could be mediated or modified by the relative presence of other AD-related abnormalities. To test this issue, separate regression models were run using 2 separate neuropathologic indexes as predictors. Lewy body abnormalities served as the first predictor (LB or Lewy neurite). The second predictor was an additional neuropathology index (amyloid burden, neuropil threads, or neurofibrillary tangles) from the same brain region. Duration of illness, last mMMSE score, and rate of cognitive decline served as the dependent measures. These regression analyses were not statistically significant, suggesting that the lack of association between LB abnormalities and clinical features was not confounded by the relative presence of other AD abnormalities.

Table 2. Simple Bivariate Correlations Between Lewy Body and Lewy Neurite Abnormalities and 3 Clinical Features

	Pearson *r*		
	Last mMMSE Score	mMMSE Score Decline	Illness Duration
Lewy body abnormalities			
Frontal cortex	–0.16	–0.17	0.22
Entorhinal cortex	0.02	–0.29	–0.29
Substantia nigra	0.07	0.02	0.31
Hippocampus	–0.12	–0.09	–0.18
Lewy neurite abnormalities			
Frontal cortex	–0.02	–0.29	–0.09
Entorhinal cortex	–0.51	0.31	0.41
Substantia nigra	–0.48	0.41	0.07
Hippocampus	–0.11	–0.10	–0.01

Abbreviation: mMMSE, modified Mini-Mental State Examination.

COMMENT

Previous research[2] using the Predictors Study cohort did not demonstrate a significant association between LB abnormalities and clinical features in postmortem cases with a confirmed diagnosis of AD, but that study used a semiquantitative rating method as opposed to a detailed quantitative neuropathologic analysis. The present study found no relation between quantitative neuropathologic indexes of LB abnormalities and clinical outcomes, including hallucinations, EPSs, illness duration, cognitive status at the last examination, and rate of cognitive decline.

A major contribution of the present study lies in the detailed neuropathologic analyses used to determine the presence and degree of LB abnormalities in 4 brain regions: the entorhinal cortex, substantia nigra, frontal cortex, and hippocampus. Both LB and Lewy neurite abnormalities were assessed using sections that were stained with antibodies to α-synuclein, which is increasingly recognized as a more specific immunostain for LB-related neuropathologic disorders.[29,30] Furthermore, we evaluated the possibility that statistical suppression may underlie the lack of association between LB abnormalities and clinical outcome. However, consistent with previous findings,[2] the association between LB abnormalities and 5 selected clinical features remained statistically nonsignificant.

We originally predicted that the presence or absence, quantity, and distribution of LB abnormalities might represent a major underlying cause of observed differences in the disease course of patients with the clinical diagnosis of probable AD. Although there had been some early reports of a relationship between LB abnormalities counts in several cortical areas and dementia severity,[13,33-35] other researchers did not find such relationships.[8,36,37] Furthermore, the neuropathologic basis of dementia is unclear even in pure DLB because neuronal loss and synaptophysin levels do not correlate with clinical symptoms.[38] In the present study, using quantitative evaluation of LB abnormalities, we found no evidence that the variability of clinical features in AD is related to the presence or degree of LB abnormalities, suggesting that "incidental" LBs in AD may be truly incidental. On the other hand, the clinically significant moiety may not be α-synuclein aggregated as LBs, per se, but rather as soluble or oligomerized forms of α-synuclein, which were not quantitated in this study.[39-41]

The present sample did not include patients encompassing the full clinical spectrum of DLB. Instead, patients in this study received a clinical diagnosis of AD and were determined to have mild-to-moderate impairments. Moreover, initially, patients were evaluated for complaints about cognitive but not motor function. Hence, the clinicopathologic relations reported herein are relevant to the question of whether clinical outcome in patients with AD varies as a function of the presence and the degree of LB abnormalities in this patient population.

The strict selection criteria limited the number of autopsy cases and, consequently, our power to see effects of even a moderate size. In light of these circumstances, liberal statistical criteria were used to determine whether the relation of LB abnormalities to distinct clinical features was significant. The actual noted effect size for any relationship was very small. Thus, it is not clear whether increasing the number of participants would have yielded an association between LB abnormalities and the selected clinical outcomes. It is possible that LB abnormalities in other brain regions (eg, the amygdala and the cingulate cortex) may be more critical. However, the detailed quantitative evaluation of LB abnormalities, careful prospective clinical follow-up, and consistency with previous findings that relied on a much larger sample size[2] suggest that the variability of clinical features in AD is not related to the presence or degree of LB abnormalities.

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