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Age and apoE associations with complex pathologic features in Alzheimer's disease

Gregory A. Jicha, MD, PhD^{1,2,7}, Joseph E. Parisi, MD^{2,3}, Dennis W. Dickson, MD^{2,4}, Ruth Cha, MS⁵, Kris Johnson, RN², Glenn E. Smith, PhD⁶, Bradley F. Boeve, MD^{1,2}, Ronald C. Petersen, PhD, MD^{1,2}, and David S. Knopman, MD^{1,2}

¹Department of Neurology, Mayo Clinic, Rochester, MN, Jacksonville, FL.

²Alzheimer's Disease Research Center, Mayo Clinic, Rochester, MN, Jacksonville, FL.

³Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, Jacksonville, FL.

⁴Department of Neurosciences, Mayo Clinic, Rochester, MN, Jacksonville, FL.

⁵Health Sciences Research, Mayo Clinic, Rochester, MN, Jacksonville, FL.

⁶Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, Jacksonville, FL.

Abstract

The risk for Alzheimer's disease (AD) is influenced by both age and ApoE status. The present study addresses the associations of age and ApoE status on complex pathologic features in AD (n=81) including coexistent cerebrovascular disease (CVD), argyrophilic grain disease (AGD), and Lewy body disease (LBD). The frequency of coexistent cerebrovascular disease increased with increasing age. Age and ApoE status were differentially associated with atherosclerosis, lacunar infarctions, and microvascular pathology. Coexistent Lewy body pathology was negatively associated with age, dropping off abruptly after age 90. The presence of an ApoE ϵ 4 allele was associated with an increased frequency of coexistent LBD. Logistic regression analyses demonstrated both dependent and independent effects of age and ApoE status on the presence of coexistent Lewy body pathology in AD. While the decreasing frequency of LBD in AD after age 90 could be partly accounted for by a lower probability of an ApoE ϵ 4 allele, the independent association with age suggests either 1) a survival effect, 2) decreased incidence with advancing age, or 3) both.

Keywords

Alzheimer's disease; cerebrovascular disease; Lewy body disease; argyrophilic grains; age; apolipoprotein E

Corresponding author: David S. Knopman, M.D., Department of Neurology, Mayo Clinic College of Medicine, 200 First Street S.W., Rochester, MN, Phone: (507) 538-1038, Fax: (507) 538-6012, e-mail: knopman.david@mayo.edu.

⁷Present address: Sanders-Brown Center on Aging, Department of Neurology, University of Kentucky College of Medicine, Lexington, KY.

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Introduction

The risk for Alzheimer's disease (AD) increases with advancing age.[30,31,33] Similar age-associated risks have been well documented for cerebrovascular disease (CVD),[18,30,33,46,65] argyrophilic grain disease (AGD),[9,53,57] and Lewy body disease (LBD),[37,50,52,60] independently. CVD, AGD, and LBD often coexist with AD pathology in individual patients and may contribute to the cognitive decline seen in AD.[3,4,17,21,26,41,49,55,58,63,64] While several studies have demonstrated an association of these pathologic features with AD, it is unclear if the age-associated risks of CVD, AGD, and LBD are dependent or independent of the age-associated increased risk for the development of AD noted in epidemiologic studies.[30,33]

The finding of multiple pathologic processes contributing to cognitive decline in the same individual is common, ranging from 50–70% in some autopsy series.[3,23,34,41,55,58,63] Age, gender, and ApoE status have all been shown to play independent roles in the development of AD, CVD, LBD and other degenerative diseases.[6,9,18,30,33,46,50,53,59,60,64] Few studies have examined demographic and genetic influences on the development of complex pathologic phenotypes in AD.[64] The frequency of coexistent CVD in AD is estimated at 30–40%, suggesting a possible shared pathogenic mechanism.[12,14,49,64] The frequency of coexistent Lewy body pathology ranges from 21% to over half of all AD cases in some series, [23,26,59] again suggesting possible shared mechanisms of intraneuronal inclusion body formation and neurodegeneration. These complex, but common, pathologic phenotypes illustrate the heterogeneity of pathologically diagnosed AD. The present study examined age and ApoE status in 81 clinically diagnosed and pathologically confirmed AD cases in relation to coexistent CVD, LBD, and AGD pathology.

Methods

Study Population

We identified all autopsy cases from January 1999 to December 2004 with clinical diagnoses of AD proximal to death, age 65 and higher, who were enrolled in the Mayo Clinic Alzheimer's Disease Patient Registry (ADPR)[47]/Alzheimer's Disease Research Center (ADRC), or who participated in a recent community based study of nonagenarians in Olmsted County, MN. [8] Inclusion criteria for this study included a clinical diagnosis of AD[38] and pathologic confirmation of this diagnosis with NIA-Reagan intermediate or high likelihood of AD.[1] These studies have been approved by the Mayo Institutional Review Board.

Clinical Evaluation

Initial clinical evaluation included detailed history and examination by a behavioral neurologist. Neurologic and neuropsychologic examinations were performed on all subjects at entry and then annually for subjects enrolled in the ADPR/ADRC programs. Clinical diagnosis was determined by a consensus committee comprised of neurologists, neuropsychologists, nurse specialists, and a geriatrician following review of all available data for ADPR/ADRC subjects and by the examining neurologist for subjects enrolled in the community-based study of nonagenarians. We used Diagnostic and Statistical Manual IV for the diagnosis of dementia [2] and the National Institute on Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for AD. [38] Cognitive assessments reported are from the last visit prior to death (typically 1 year) and include Mini-Mental State Exam (MMSE)[20] and Clinical Dementia Rating (CDR) Score. [40] Unified Parkinson's Disease Rating Scale (UPDRS) scores were available on 61 of the 81 subjects presented, including 41 of 56 subjects without (73%), and 20 of 25 subjects with

neuropathological LBD (80%). ApoE genotyping was performed on blood samples as described previously.[48]

Neuropathologic Evaluation

The brains were processed according to the protocol of the Mayo ADRC Neuropathology Core in accordance with the recommendations of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD).[39] Pathologic diagnoses were based on evaluation of mid-frontal gyrus, inferior parietal lobule, superior temporal gyrus, anterior cingulate gyrus, occipital cortex (Brodmann's area 17), hippocampus at the level of the lateral geniculate body, amygdala and entorhinal cortex at the level of the mammillary bodies, nucleus basalis, cerebellum, dorsomedial thalamus with subthalamic nucleus, midbrain with substantia nigra. Routine histochemical stains performed on all sections included hematoxylin-eosin (H&E) and modified Bielschowsky silver impregnation, which was used for assessment of CERAD,[39] NIA-Reagan,[1] and Braak staging[10] of AD pathology.

α -synuclein immunohistochemistry (LB509, 1/200 dilution; Zymed, South San Francisco, CA) was used to identify Lewy bodies and Lewy neurites in the anterior cingulate gyrus, hippocampus, amygdala, and midbrain including the substantia nigra and locus coeruleus according to consensus guidelines for the pathologic diagnosis of Dementia with Lewy bodies. [36,37] Cases demonstrating Lewy body pathology extending into the anterior cingulate gyrus, underwent further α -synuclein immunohistochemical analysis on sections from the frontal, temporal and parietal cortex to confirm the presence of neocortical Lewy body pathology. Lewy body pathology was then categorized as either absent, brainstem, limbic, or neocortical, representing stage 0, 1, 2, 3 respectively.

Phosphorylated tau immunohistochemistry (AT8, 1/1000 dilution; Endogen, Woburn, MA) was performed on sections including hippocampus at the level of the lateral geniculate body, amygdala, anterior cingulate, frontal, temporal, parietal, and occipital cortices. Argyrophilic grain disease was visualized with both Gallyas stain and AT-8 and included as a pathologic diagnosis only if there was significant involvement of the medial temporal lobe, as well as evidence for tau-positive coiled bodies in white matter and "ballooned" neurons in the amygdala.[9] The presence or absence of AGD is presented as a dichotomous variable in this analysis.

Size, location, and histologic age of large and small vessel infarcts were recorded. Acute or subacute infarcts were not considered clinically significant with respect to chronic antemortem neurologic features. Microvascular disease (arteriosclerosis) intracranial atherosclerosis (circle of Willis), and amyloid angiopathy were assessed using semi-quantitative grading scales according to the National Alzheimer Coordinating Center protocol (available at <https://www.alz.washington.edu/NONMEMBER/PDF/npded2004.pdf>). These assessment measures have not been validated or standardized across sites for the assessment of vascular pathology in submitted data. Mayo criteria for grading arteriosclerosis follows the guidelines of Esiri et al, as follows: grade 0-no pathological changes present; grade 1-minimal lipohyalinosis and widening of the perivascular space not explained fully by fixation and processing artifact; grade 2-mild to moderate lipohyalinosis and thickening of arteriolar wall without myelin pallor or microvascular infarcts; grade 3-moderate to severe lipohyalinosis, without myelin pallor or microvascular infarcts; grade 4-severe lipohyalinosis or the presence of microinfarcts related to atherosclerotic disease. Microinfarcts were graded using the dichotomous presence or absence of these findings in the examined specimens without the use of a grading standard. Microvascular infarcts were included in the description of arteriosclerotic disease as defined above. Mayo criteria for grading atherosclerosis includes: grade 0-no atherosclerosis, grade 1- 0 to 25% vascular occlusion; grade 2- 25 to 50% vascular occlusion; grade 3- 50–75% vascular occlusion; grade 4- 75–100% vascular occlusion. Mayo

criteria for grading amyloid angiopathy includes: grade 0-no amyloid present; grade 1-minimal amyloid present in leptomeningeal vessels only; grade 2- Mild to moderate amyloid present in meningeal and small parenchymal vessels; grade 3- severe amyloid present in meningeal and small as well as larger parenchymal vessels; grade 4- severe amyloid angiopathy with micro-hemorrhage. The diagnosis of cerebrovascular disease (CVD) applied in this study includes all cases with large vessel or lacunar infarcts and any cases with severe (grade 3 or higher) atherosclerosis, arteriosclerosis, or amyloid angiopathy regardless of the presence or absence of infarcts.

Statistical Analysis

Spearman correlations, Student's t-tests, Mann-Whitney U-tests, Fisher exact tests, univariate and multivariate Logistic regression analyses were used to assess age-related trends and the influence of the Apolipoprotein E ϵ 4 allele on coexistent pathologic features in AD where appropriate. While most studies investigating complex neuropathological phenotypes of degenerative disease have reduced the complexity of data by generating dichotomous variables for the presence or absence of CVD and LBD or presented only isolated components of CVD [3,5,7,13,19,25,29,54], we have chosen to present a detailed assessment of distinct pathological features and staging in order to more fully present our data and explore the associations between the component features of CVD and staging of CVD and LBD. As such the analysis should be considered exploratory in its interpretation. Given the significant number of correlational and comparative analyses required to include a full descriptive analysis of all relevant pathological features, we acknowledge the likelihood of type I error in the results. A true Bonferroni correction would set the p-value < 0.002 , which would exclude many of the findings as insignificant. Such an analysis would introduce the confound of excluding potentially significant results (type II error). P-values less than 0.05 were considered statistically significant for the purposes of complete presentation of the neuropathologic data herein. We hope that the discerning reader will take these considerations into account in their personal interpretation on the data presented. Further analyses on more extensive datasets will be required to address these issues and further confirm the present exploratory findings.

RESULTS

Eighty-one subjects with both clinical and neuropathologic AD are presented. There were 2 sexagenarians, 13 septuagenarians, 32 octogenarians, 26 nonagenarians, and 8 centenarians who met inclusion criteria. Demographic, genetic (ApoE status), clinical, and neuropathologic variables are presented in Table 1.

By definition, all cases met NIA-Reagan criteria for AD; 17 were classified as intermediate and 64 as high likelihood of AD. All cases with LBD showed involvement of limbic ($n=14$) or cortical structures ($n=11$) in addition to the involvement of brainstem nuclei. We found no cases with isolated brainstem Lewy body disease. UPDRS scores ranged from 0–23 across the subjects studied. UPDRS scores greater than 0 were found in 44 of the 61 subjects with available data and did not differ significantly between subjects with and without LBD ($p=0.69$, Mann-Whitney U-test). Only 4 of the 11 AD cases with neocortical LBD showed evidence for extrapyramidal features on last examination. None of the cases presented were assigned a primary diagnosis of the Lewy body variant of AD based on our case selection criteria of primary clinical diagnosis as probable AD.

The relationship between age, ApoE ϵ 4 status, and coexistent neuropathologic features in AD (Table 2) are presented graphically in Figure 1 and Figure 2. Individuals with an ApoE ϵ 4 allele were younger than ApoE ϵ 4 negative subjects (86.0 ± 6.9 vs 90.9 ± 7.2 , $p=0.004$, t-test). That is, most of the very elderly AD patients were ApoE ϵ 4 negative.

In contrast, those with CVD (89.3 ± 7.5 vs 84.2 ± 8.7 , $p=0.017$, t-test) and lacunar infarcts (91.2 ± 8.3 vs 85.4 ± 7.1 , $p=0.0011$, t-test) were older than those without those vascular features. Likewise, increasing severity of atherosclerosis correlated with advancing age. As shown in Figure 2, the fraction of AD patients with one or more manifestations of CVD went from none to nearly 100% across the age spectrum of 65 to 100+. The presence of an ApoE $\epsilon 4$ allele was significantly associated with grade of arteriosclerosis and microvascular pathology. There was no association between amyloid angiopathy and either age or ApoE status (table 2).

Argyrophilic grain pathology also increased with advancing age in these AD patients, although the trend was not significant (Figure 2).

Individuals with LBD pathology were also younger than those without LBD pathology (84.6 ± 7.6 vs 89.3 ± 8.0 , $p=0.016$, t-test). Figure 2 shows the declining proportion of LBD-pathology-positive AD patients with advancing age. Univariate logistic regression models demonstrated that ApoE $\epsilon 4$ status and age <90 were significantly associated with coexistent LBD in AD (Table 3).

DISCUSSION

Both cerebrovascular and argyrophilic grain disease increased in frequency with increasing age in subjects with moderately severe or severe AD before stabilizing in the 10th and 11th decades of life (Figure 2). In contrast, the frequency of ApoE $\epsilon 4$ positive AD and coexistent LBD in AD declined over the age spectrum we studied.

While some features increased in frequency into the 9th through 11th decades, the decline in others raises the possibility of a selective mortality effect of ApoE $\epsilon 4$ genotype and LBD pathology. If this is the case, then it remains to be explained why AD that is ApoE $\epsilon 4$ negative and LBD negative is not as virulent a condition as ApoE $\epsilon 4$ positive AD or AD with coexistent LBD.

Most series that have evaluated coexistent LBD in AD, also termed the Lewy Body Variant of AD (LBV), demonstrate a mean age nearly a decade below that reported in this series. [37, 50, 52, 60] The trend for decreasing frequency of coexistent LBD in AD with advancing age seen in this study could be easily missed if a younger cohort were studied. Similar analyses of coexistent LBD in AD and other complex pathologic features in the oldest-old have not been reported.

The increase in frequency of cerebrovascular disease with advancing age seen in this study was expected, as stroke, atherosclerosis, and microvascular disease in the elderly result from cumulative vascular insults occurring over time. [11, 18, 27, 30, 32, 33, 46] While only lacunar disease and atherosclerosis of the circle of Willis increased significantly with advancing decade of life, all measures of cerebrovascular disease analyzed in this study showed this same trend (albeit this trend did not reach statistical significance for large vessel strokes or arteriosclerosis and microvascular disease), with the exception of amyloid angiopathy which was essentially constant across ages. This was not surprising as AD itself is a major risk factor for amyloid angiopathy and may have overshadowed the effect of age on the development of this pathologic feature in this series. [35, 62] Others have reported a lack of strong association between ApoE and amyloid angiopathy, but see Olichney 1996 who found a strong relationship between ApoE and amyloid angiopathy. [43]

There is much current interest in the association between cerebrovascular disease and AD. [14, 64] It has been suggested by some that vascular insults may be causative in the development of AD. [15, 16, 61] While this is debated, it is clear from epidemiologic studies that AD and cerebrovascular disease share many risk factors. [11, 15, 16, 42, 61, 64] Our data further support

the association of cerebrovascular disease with AD [11,15,16,42,61,64], and further demonstrates an increase in frequency to 100% in centenarians. The detailed assessment of vascular pathology in this study and differences in criteria for CVD between studies, likely contributed to a higher sensitivity for the detection of coexistent cerebrovascular disease in AD than that seen in previous studies. Further work in the area of cerebrovascular contributions to cognitive decline in the elderly and its relationship to AD is warranted.

Argyrophilic grain pathology is a common finding in aged brains regardless of cognitive status. [9,21,53,57] Age appears to be the major risk factor for the development of this pathologic feature in unselected autopsy series with heterogeneous pathological diagnoses.[9,53,57] The lack of a statistically significant relationship between advancing age and AGD in the AD cases presented may be related to either the small number of subjects in this series, a possible interaction between AGD and AD pathology that is stronger than the association with age, or methodological limitations in identifying AGD pathology in the background of high density neuritic pathology of the Alzheimer-type. Further elucidation of this relationship using antibodies that are relatively selective for four-repeat tau in AGD could be useful in for future analyses of this type.[56] The finding of AGD in cognitively normal individuals at autopsy has raised some speculation regarding the contribution of AGD, or lack thereof, to cognitive decline in the elderly. AGD, however, is often the sole pathologic feature seen in the brains of some individuals with clinical dementia suggesting that it can play an important role in clinical cognitive decline in the elderly. [9,21,53,57] Efforts at developing a staging system for AGD that may correlate with clinical status have been proposed and may help elucidate the role of AGD in the development of dementia in the elderly.[9,53,57]

The main pathologic features of AGD are tau-positive curvilinear structures (grains) that can be seen throughout the neuropil in affected brains with a predilection for the amygdala, hippocampus, cingulate and medial temporal cortices. [9,53,57] As such, the biochemical composition and anatomical distribution of AGD overlaps significantly with that seen in AD. This is often a confound in the detection of AGD in cases with significant AD pathology. The frequency of coexistent AGD in AD is likely under-reported secondary to these issues.[21] Nonetheless, the finding of coexistent AGD in one quarter of the AD cases presented is consistent with previous reports in the literature [9,21,53,57] and suggests that AGD needs to be considered as a common co-morbidity in AD.

Over the age spectrum we studied, LBD pathology decreased. In contrast, several studies have reported on the association of LBD pathology with age and have shown a positive correlation. [28,50–52,60] This contrasts sharply to the findings of the present study. The difference is likely related to a much younger mean age in most cohorts that have been examined. A previous study analyzing the frequency of LBD in a community based cohort, included 23 nonagenarians.[60] An age-dependent increase in the frequency of LBD of approximately 7% per year was reported. However, the prior study [60] also showed an abrupt drop-off in LBD frequency after age 90. The authors did not comment on this finding, but instead focused on the age-related increase in frequency of LBD seen in the younger cases. The decline in frequency of LBD after age 90 could be due to several mechanisms. If LBD increased mortality at younger ages, fewer persons with LBD would survive into the 10th decade of life (a negative survival effect). A second possibility would be that LBD is more like frontotemporal lobar degenerations in peaking at an earlier age and simply not invariably increasing with advancing age like AD. Or, both mechanisms could be operative. Our data are insufficient to answer this question at present, but it is clear that further exploration of this finding is warranted.

The presence of neocortical LBD in 11 of these cases raises the possibility that the AD pathology may be a secondary contributor to the cognitive decline and that the LBD is the primary pathology.[37] Our data further confirm the findings of Parkkinen and colleagues who

have demonstrated convincingly that pathological LBD and the presence of extrapyramidal signs and symptoms are not always coincident. [44,45] The cases themselves were selected on the basis of a clinical diagnosis of AD[38] and the presence of sufficient AD pathology to confirm this clinical diagnosis.[1] The argument over which pathology is primary is moot, as both likely contribute to the clinical picture of dementia.

The data also show a significant association of ApoE ϵ 4 with coexistent LBD in AD. This finding has been previously reported in several series. [22,24,59] The age-associated decline in ApoE ϵ 4 allele frequency in AD is presumed to be due to a survival effect.[6] The same association with age is seen in the present study with ApoE ϵ 4 allele frequency dropping from 0.39 in septagenarians to 0.14 in centenarians in this series. This decline in ApoE ϵ 4 allele frequency is at least partly responsible for the age-related decline in coexistent LBD in AD seen in this study. While both age and ApoE status were shown to contribute to the decline in LBD in AD seen with advancing age, the effect of age appeared to have a stronger influence.

The strengths of this study include the large number of cases, the broad age spectrum, and the use of prospective semiquantitative neuropathological examinations. However, it would have been stronger if more subjects under age 70 were available. A larger number of men might have allowed us to look at gender and age interactions. As our subjects were entirely European-American ethnicity, it is uncertain whether our findings can be generalized to other ethnic groups. Potential selection bias related to autopsy consent may have also influenced the findings in this study. Lastly, while the inclusion of such extensive semiquantitative neuropathological data allows a more complete understanding of the complexity of coexistent pathological features in AD, the likelihood that at least one of the statistical outcomes represents a false positive result (Type I error) needs to be considered in the interpretation of the data from this exploratory study. Further analyses of demographic, genetic, and environmental influences on the development of complex pathological phenotypes of AD are needed.

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Figure 1.
The frequency of cases that are ApoE ϵ 4 positive declines with advancing age in AD.

Figure 2.

The relative frequency of AD cases with coexistent CVD ($p=0.017$) and AGD ($p=0.20$, n.s.) increase with advancing age. In contrast, the relative frequency of AD cases with coexistent LBD decreases with advancing age ($p=0.016$).

Table 1

Demographics, clinical data, and pathologic features

Variable	Value
Age (mean years)	87.9 (s.d. 8.1)
Gender (M:F)	21:60
ApoE ε4 (allele frequency)	0.34
CDR global (mean score)	2.2 (s.d. 0.9)
CDR SOB (mean score)	13.4 (s.d. 5.4)
MMSE (mean score)	16.6 (s.d. 7.4)
Time from last evaluation to death (mean years)	1.0 (s.d. 1.0)
CERAD (mode)	Definite
NIA-Reagan (mode)	High likelihood
Braak Stage (mean)	4.5 (s.d. 1.1)
Coexistent LBD (frequency)	0.31
Coexistent AGD (frequency)	0.25
Coexistent CVD (frequency)	0.72
Large vessel strokes (frequency)	0.11
Lacunar infarcts (frequency)	0.43
Arteriosclerosis and microvascular disease (mean severity score)	2.1 (s.d. 0.9)
Circle of Willis atherosclerosis (mean severity score)	1.7 (s.d. 0.8)
Amyloid angiopathy (mean severity score)	1.5 (s.d. 1.0)
Any pathology in addition to Alzheimer's (frequency)	0.81

Abbreviations: CDR, Clinical Dementia Rating Scale; SOB, sum of boxes; MMSE, Mini-Mental State Examination; ApoE, apolipoprotein E; CERAD, Consortium to Establish a Registry for Alzheimer's Disease neuropathological criteria for AD; NIA-Reagan, National Institutes of Aging and Reagan Institute Working group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease neuropathological criteria for AD; Braak Stage, Braak and Braak staging system for neurofibrillary tangles; CVD, presence of vascular lesions or stroke; LBD, Lewy Body Disease; AGD, Argrophilic Grain Disease.

Table 2

Associations of age and ApoE ε4 with clinical measures and pathologic features (values reported are p-values for the indicated statistical test used. r values are also included for Spearman correlations in parentheses)

Demographic, Clinical, and Pathologic Variables	Age	ApoE ε4 allele
Gender	0.090 [§]	0.86 [€]
ApoE ε4 allele	0.018 [§]	—
LBD (present or absent)	0.016 [§]	0.021 [€]
LBD (semi-quantitative assessment of extent of pathology) *	0.019 (r= -0.26) [‡]	0.026 [‡]
AGD (present or absent)	0.20 [§]	0.18 [€]
CVD (present or absent)	0.017 [§]	0.13 [€]
Large vessel infarcts (present or absent)	0.14 [§]	0.52 [€]
Lacunar infarcts (present or absent)	0.0011 [§]	0.12 [€]
Arteriosclerosis and microvascular disease (semi-quantitative assessment of extent of pathology)	0.56 (r=0.07) [‡]	0.014 [‡]
Atherosclerosis (semi-quantitative assessment of extent of pathology)	0.022 (r=0.25) [‡]	0.33 [‡]
Amyloid angiopathy (semi-quantitative assessment of extent of pathology)	0.92 (r= -0.01) [‡]	0.45 [‡]
Any pathology (present or absent)	0.61 [§]	0.42 [€]

Abbreviations: ApoE, apolipoprotein E; CVD, dichotomized presence of severe vascular lesions or stroke; LBD, Lewy Body Disease; AGD, Argyrophilic Grain Disease.

* 0=no LBD, 1=brainstem LBD only, 2=limbic involvement of LBD, 3=neocortical LBD

[§]Students t-test

[‡]Spearman correlation

[‡]Mann-Whitney u-test

[€]Fisher exact test

Table 3

Age and Apo E influence coexistent LBD in AD (univariate and multivariate regression analyses)

Variable	Odds ratio	95% CI	p-value
Age <90 (unadjusted)	5.94	1.65, 21.35	0.0064
Apo E e4 (unadjusted)	3.62	1.19, 10.95	0.023
Age <90 (adjusted for Apo E status)	3.82	1.01, 14.48	0.049
Apo E e4 (adjusted for age)	2.64	0.82, 8.45	0.10

Abbreviations: ApoE, apolipoprotein E; LBD, Lewy Body Disease