APOE, vascular pathology, and the AD brain

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Abstract—*Objective:* To use neuropathologic data to examine the association between *APOE* genotype and cerebrovascular lesions commonly found in Alzheimer disease (AD), as well as neuritic senile plaque (SP) and neurofibrillary tangle (NFT) burden. *Methods:* The sample comprised brains from 96 men and 3 women who fulfilled NIA-Reagan criteria for intermediate to high likelihood of AD. Region-specific and global measures of gross cerebrovascular disease, arteriolosclerosis, white matter lesions, microinfarcts, amyloid angiopathy, neuritic SP, and NFT burden were compared among those who had at least one *APOE*-ε4 vs those who did not. Pairwise rank-order correlations between measures were calculated. The association between *APOE* ε4 status and measures of vascular and AD pathology, adjusting for age at death, sex, brain weight, and Braak stage, were evaluated. *Results: APOE*-ε4 was not associated with gross cerebrovascular pathology. Compared to those who were negative, brains from ε4 individuals had a greater degree of small vessel arteriolosclerosis ($p = 0.04$) and perivascular macrophage infiltration ($p = 0.06$), but not other markers of small vessel disease or white matter myelin loss. Microinfarcts in the deep nuclei were associated with ε4 ($p = 0.009$), whereas cortical and subcortical microinfarcts were not. There was a trend toward association between *APOE* genotype and amyloid angiopathy ($p = 0.08$), and ε4 was associated with neuritic SP burden, but not NFT. *Conclusion: APOE*-ε4 is associated with small vessel arteriolosclerosis, microinfarcts of the deep nuclei, neuritic senile plaque density, and amyloid angiopathy in patients with autopsy-proven Alzheimer disease (AD). These results suggest a role for ε4 in some of the microvascular changes commonly found in AD and are consistent with a potential amyloidogenic role for ε4.

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There is considerable evidence from the epidemiologic, clinical, and pathologic literature that cerebrovascular disease may play a key role in Alzheimer disease (AD) pathogenesis, progression, and clinical expression.[1,2] Neuropathologic data show that more than 30% of AD cases exhibit some cerebrovascular pathology, and that certain vascular lesions such as cerebral amyloid angiopathy, microvascular degeneration, and periventricular white matter lesions are evident in almost all cases of AD that come to autopsy.[3] Furthermore, the presence of vascular pathology appears to modify the clinical expression of AD: in the Nun Study, fewer neuropathologic lesions of AD resulted in dementia in subjects with lacunar infarcts in the basal ganglia, thalamus, or deep white matter than in those without infarcts.[4] Exactly how vascular lesions are related to AD pathogenesis remains to be defined.

More than a decade after initial reports that AD has a strong genetic basis, the ε4 allele of *APOE* remains the most consistent AD genetic susceptibility factor.[5] Although the subject of intense research activity, the exact mechanisms through which *APOE* exerts its influence on AD risk remain unknown: modulation of amyloid precursor protein (APP) processing[6]; β-amyloid protein synthesis,[7] binding,[8,9] aggregation,[10] deposition, and clearance[11,12]; tau phosphorylation[13]; and lipid handling[6] have been suggested in the neurobiologic literature.

APOE also plays an important role in lipoprotein metabolism—specifically, the functional effects of the ε2/ε3/ε4 polymorphism are mediated through hepatic binding, uptake, and catabolism of chylomicrons, chylomicron remnants, very low density lipoprotein (VLDL), and high density lipoprotein (HDL) species. Indeed, ε4 is associated with increased risk for cardiovascular disease,[14] ischemic[15] and hemorrhagic[16] stroke, though not with carotid artery atherosclerosis.[17]

In this study we examined brains of patients with pathologically proven AD in order to evaluate the association between *APOE* genotype and cerebrovascular lesions seen at autopsy. We examined infarcts, hemorrhage, atherosclerosis, arteriosclerosis, amyloid angiopathy, myelin loss of the deep white matter, microinfarcts and other markers of small vessel pathology (i.e., perivascular macrophage infiltration, perivascular dilatation, perivascular rarefaction, perivascular hemosiderin deposition, and vascular mineralization), as well as AD lesions (neurofibrillary tangle and senile plaque burden).

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Table 1 *General description of sample (n = 99)*

Mean death age, y (SD)	75.1 (7.0)
Male (%)	96 (97.0)
Mean brain weight, g (SD)	1,183.6 (119.9)
Braak stage	
Braak Stage III (n = 4)	1 "pure" AD
	1 AD + at least one infarct or lacune
	2 AD + dementia with Lewy bodies
Braak Stage IV (n = 7)	3 "pure" AD
	2 AD + at least one infarct or lacune
	2 AD + dementia with Lewy bodies
Braak Stage V (n = 24)	20 "pure" AD
	2 AD + at least one infarct or lacune
	2 AD + dementia with Lewy bodies
Braak Stage VI (n = 64)	47 "pure" AD
	10 AD + at least one infarct or lacune
	7 AD + dementia with Lewy bodies
Mean neuritic SP score (SD)	12.0 (3.2)
Mean NFT score (SD)	14.4 (2.0)
Mean amyloid angiopathy score (SD)	1.7 (2.9)
Mean WML score (SD)	30.7 (10.9)
Mean microinfarct score (SD)	1.9 (3.4)
APOE ε4+ (%)	63 (63.6)

AD = Alzheimer disease; SP = senile plaques; NFT = neurofibrillary tangles; WML = white matter lesions.

Methods. The sample was drawn from the Boston University AD Center (BU ADC) Brain Bank for which the primary referral source is a late-stage unit at the Edith Nourse Rogers VA Medical Center (Bedford, MA), and comprised predominantly white men with mean age at death of 75 years (SD = 7.0) who fulfilled NIA-Reagan criteria[18] for intermediate to high likelihood of AD (see table 1 for sample characteristics).

The neuropathologic assessment was performed by a single neuropathologist (A.C.M.) who was blinded to the subject's clinical history and genotype information using well-established brain banking protocols.[19] Briefly, the brains were received fresh, photographed, and weighed. The gross neuropathologic findings were recorded, including the location and volume of all infarcts, hemorrhages, and lacunes, and the degree of atherosclerosis in the circle of Willis. The tissue was fixed in 4% periodate-lysine-paraformaldehyde (PLP) at 4 °C for at least 2 weeks prior to the preparation of tissue sections for paraffin blocks. Ten-micron sections from 16 brain regions were examined: olfactory bulb; midbrain at the level of the red nucleus; precentral cortex; postcentral cortex; inferior parietal cortex; anterior cingulate gyrus; middle frontal cortex; caudate, putamen, and accumbens; superior temporal lobe; amygdala with entorhinal cortex; globus pallidus, insula, and substantia innominata; hippocampal formation at the level of lateral geniculate nucleus; thalamus with subthalamic nucleus; calcarine cortex; upper pons; and cerebellum with dentate nucleus. Sections were stained with Luxol fast blue, hematoxylin and eosin, and Bielschowsky silver. Multiple sections from each case were also stained with either alpha-synuclein (Chemicon, affinity purified polyclonal, 1:3000, pretreated in formic acid) or ubiquitin (Dakocytomation, 1:400), and the calcarine cortex was immunostained for amyloid beta protein (Dako, 6F-three-dimensional, 1:500, pretreated in 90% formic acid for 2 minutes).

The density of NFT was rated semiquantitatively in seven regions (inferior parietal [BA 40], middle frontal [BA 8], superior temporal [BA 22], calcarine [BA 17], amygdala, entorhinal cortex, and hippocampus). All determinations were made in areas of maximum involvement at a magnification of 200x using the average count from three microscopic fields. The semiquantitative density of neuritic plaques (NP) was determined in the same regions using guidelines established by Consortium to Establish a Registry for Alzheimer's Disease (CERAD) wherein a 1+ rating corresponded to a CERAD rating of sparse, a 2+ score corresponded to a CERAD rating of moderate, and a 3+ or 4+ score to a CERAD rating of frequent plaques.[20] Global measures of NFT and SP burden were then derived by summing scores across the areas sampled.

Neuropathologic diagnosis for AD was established based on NIA-Reagan criteria,[18] which includes Braak and Braak hierarchical assessment of neurofibrillary tangle pathology[21] and CERAD assessment of neuritic senile plaque burden.[20]

The severity of amyloid angiopathy was evaluated using amyloid beta immunostained sections of the calcarine cortex in a manner modified from Vonsattel et al.[22] and Esiri et al.[23] If no cerebral vessels showed immunopositivity for beta amyloid, the area is scored as 0. If amyloid is restricted to a rim around smooth muscle fibers in the media of occasional normal vessels, the area is graded as 1+. If the media is thicker than normal and circumferentially replaced by amyloid in a few vessels, the area is rated 2+. If there is widespread medial thickening and circumferential amyloid deposition with a small halo of immunoreactivity in the surrounding parenchyma, and there may be a focus of wall leakage as evidenced by fresh hemorrhage or hemosiderin-laden macrophages, or occlusion, or recanalization, the area is scored as 3+.

Microinfarcts were defined as cavitated microinfarcts or encephalomalacic lesions, 2 mm or smaller in greatest dimension, not identifiable with certainty on gross inspection of the brain; or non-cavitated microinfarcts, focal gliotic areas without a cystic cavity, were counted in Rolandic, inferior parietal, superior temporal, and calcarine cortices and their corresponding underlying white matter, hippocampus, entorhinal cortex, brainstem and deep nuclei, including caudate, putamen, globus pallidus, and thalamus. The number of microinfarcts was recorded semiquantitatively in each region: 0 = no microinfarcts; 1+ = 1 to 3 microinfarcts; 2+ = 4 to 8 microinfarcts; 3+ = 9 to 19 microinfarcts; 4+ = ≥20 microinfarcts.

Microvascular pathology was further assessed by rating subcortical myelin loss in the deep white matter of the same cortical regions, as judged by gross inspection of the Luxol fast blue, hematoxylin and eosin stained slide and rated semiquantitatively on a scale from 0 to 3. Subcortical myelin loss was judged by gross inspection of the Luxol fast blue, hematoxylin and eosin stained slide and rated semiquantitatively. Myelin loss was typically accompanied by loosening of tissue, loss of nerve fibers, and gliosis in the white matter. If the area to be evaluated contained an infarct, the area was omitted from the analysis. In these white matter regions and in the deep nuclei, perivascular rarefaction, or the degree to which the tissue was attenuated around small blood vessels, dilatation of the perivascular spaces, perivascular macrophage infiltration, vascular mineralization, and arteriolosclerosis, or fibrohyaline thickening of arteriolar walls, were also evaluated semiquantitatively.

Global measures of microinfarcts, markers of small vessel disease, and myelin loss in the deep white matter were derived by summing scores across the areas sampled.

The distributions of vascular and AD pathology measures (considered singly) among brain samples from patients who were ε4+ (ε4 homozygotes and heterozygotes) and ε4- (subjects lacking an ε4 allele) were compared using the Wilcoxon test. Pairwise correlations between global measures were calculated using the Spearman rank-order correlation statistic. Analysis of covariance (ANCOVA) was used to evaluate the association between ε4 status and the global measures, adjusting for age at death, sex, brain weight, and Braak stage. Since this study is largely exploratory,

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we used an alpha level of 0.05 in interpreting these results and have made no adjustments for multiple testing.

Results. The sample for the current study comprised 97 men and 2 women with a mean age at death of 75 years (SD = 7.0). Nearly two-thirds (63.6%) of the subjects had at least one *APOE* ε4 allele. All met NIA-Reagan criteria for intermediate to high likelihood of AD. The mean brain weight was 1183.6 g (SD = 119.9). Most subjects had advanced AD: 90% were in Braak Stage V or VI; and mean NFT score was 14.4 and mean neuritic SP score was 12 (i.e., severe NFT and SP burden in every region examined). Amyloid angiopathy in the calcarine cortex was observed in 90% of the subjects (mean score = 1.7), and markers of small vessel disease were common (mean score of 30.7, corresponding roughly to mild ischemia in every region examined). Microinfarcts were rare (see table 1).

APOE and cerebrovascular pathology. Presence of at least one *APOE* ε4 allele was not associated with measures of any gross cerebrovascular pathology, gross cerebral hemorrhage, infarction, or atherosclerosis of the major basal surface arteries. ε4 was associated with arteriolosclerosis (ε4(−) mean score = 7.3 [SD = 3.4] vs ε4(+) mean score = 8.2 [SD = 3.0]; $p = 0.04$) and perivascular macrophage infiltration (ε4(−) mean score = 7.3 [SD = 3.0] vs ε4(+) mean score = 7.7 [SD = 2.3]; $p = 0.06$), but not with myelin loss in the deep white matter, perivascular rarefaction or dilatation, or vascular mineralization (see figures 1 and 2). The global measure for small vessel pathology was not associated with ε4 status ($p = 0.65$). One component measure of cerebral microinfarcts attributable to small vessel disease—cavitated microinfarcts in the deep nuclei ($p = 0.009$)—was found to be associated with ε4 status, whereas the global measure was not (ε4(−) mean score = 1.3 [SD = 2.0] vs ε4(+) mean score = 2.3 [SD = 3.9]; $p = 0.23$; see figure 2). There was a trend toward association between amyloid angiopathy and *APOE* genotype (ε4(-) mean score = 1.5 [SD = 0.9] vs ε4(+) mean score = 1.8 [SD = 1.1]; $p = 0.08$; see figure 2).

APOE and AD pathology. *APOE* ε4 status was not associated with summary and region-specific measures of NFT burden in this sample: the mean NFT score among those with no ε4 alleles was 14.6 (SD = 2.0), whereas it was 14.4 (SD = 2.0) among those with at least one ε4 allele ($p = 0.60$; see figure 2). By contrast, ε4 status was associated with the summary measure of senile plaque burden (ε4(−) mean score = 11.4 [SD = 3.4] vs ε4(+) mean score = 12.3 [SD = 3.1]; $p = 0.06$; see figure 2). In the temporal lobe, this association was seen in brains of individuals who had died at age 74 years or greater (the median death age) but not in those belonging to the younger age group (old group Wilcoxon $p = 0.02$; young group Wilcoxon $p = 0.82$; overall Wilcoxon $p = 0.11$). In the hippocampus 54.1% of those with an ε4 allele had severe to very severe hippocampal SP burden, compared to 37.5% of those without (exact $p = 0.06$). Considered on an ordinal scale the association between ε4 status and hippocampal SP burden was also significant (Wilcoxon $p = 0.04$), and the adjusted ordinal OR for ε4 (+) vs ε4 (−) was 1.99 (95% CI = 1.05 to 3.76). *APOE*-ε4 status was associated with increased SP burden in the entorhinal cortex as well (Wilcoxon $p = 0.02$; adjusted ordinal OR = 2.09, 95% CI = 1.07 to 4.10). *APOE*-ε4 status was not associated with SP burden in the amygdala (Wilcoxon $p = 0.18$).

AD lesions and cerebrovascular pathology. An examination of pairwise correlations revealed that senile plaque burden was highly correlated with neurofibrillary tangle burden (Spearman $\rho = 0.57$, $p < 0.0001$). Among vascular lesions, global measures of small vessel disease scores were moderately correlated with microinfarct scores (Spearman $\rho = 0.25$, $p < 0.01$), but not with amyloid angiopathy, which in turn was not correlated with either microinfarct or white matter lesion measures. None of the vascular measures (including myelin loss regionally or globally) were correlated with NFT or SP burden (table 2).

Discussion. In this study, we examined the association between *APOE* genotype (persons having at least one ε4 allele vs those with other *APOE* genotypes), status, macroscopic and microscopic vascular lesions, and AD pathology. We found that ε4 was associated with higher scores on global measures of several indicators of small vessel disease, namely arteriolosclerosis and perivascular macrophage infiltration, microinfarcts in the deep nuclei, and amyloid angiopathy. Furthermore, ε4 was associated with greater neuritic SP but not NFT burden. No correlation between large or small vessel disease or myelin loss and AD pathology was apparent in our sample.

Several recent studies have emphasized microvascular pathology as a major substrate of dementia in the elderly.[23-26] One study of demented and nondemented elderly subjects without significant AD pathology found that severe cribriform change and microinfarcts in the subcortical white matter and deep nuclei were associated with dementia and might represent a crucial source of cerebral damage relevant to dementia.[23] The observation in a group of 285 elderly men of Japanese descent of equal proportions of demented individuals with microinfarcts in the neocortex and basal ganglia and of demented individuals with AD lesions suggests that the role of microvascular injury in the pathogenesis of dementia may be approximately equal to that of AD.[26] Another study of 33 subjects reported a significant correlation between the severity of amyloid angiopathy and neuropsychological assessment of cognitive impairment.[25] Similarly, vascular amyloid and white matter pallor, but not microinfarcts, were associated with dementia in an examination of 101 nondemented and mildly demented elderly subjects.[27] The neuropathologic analysis of concurrent vascular pathology in AD is, therefore, a natural subject for investigation.

Arteriolosclerosis, which is also referred to as fibrohyalinosis or lipohyalinosis, is one of the most common cerebrovascular diseases of the small blood vessels in aging and AD.[23,24,28,29] Histopathologic changes of arteriolosclerosis include intimal deterioration, smooth muscle degeneration, fibrothyalinotic thickening of the vessel wall, and narrowing of the vascular lumen. Perivascular macrophage infiltration is often found in conjunction with arteriolosclerosis and is referred to as a manifestation of

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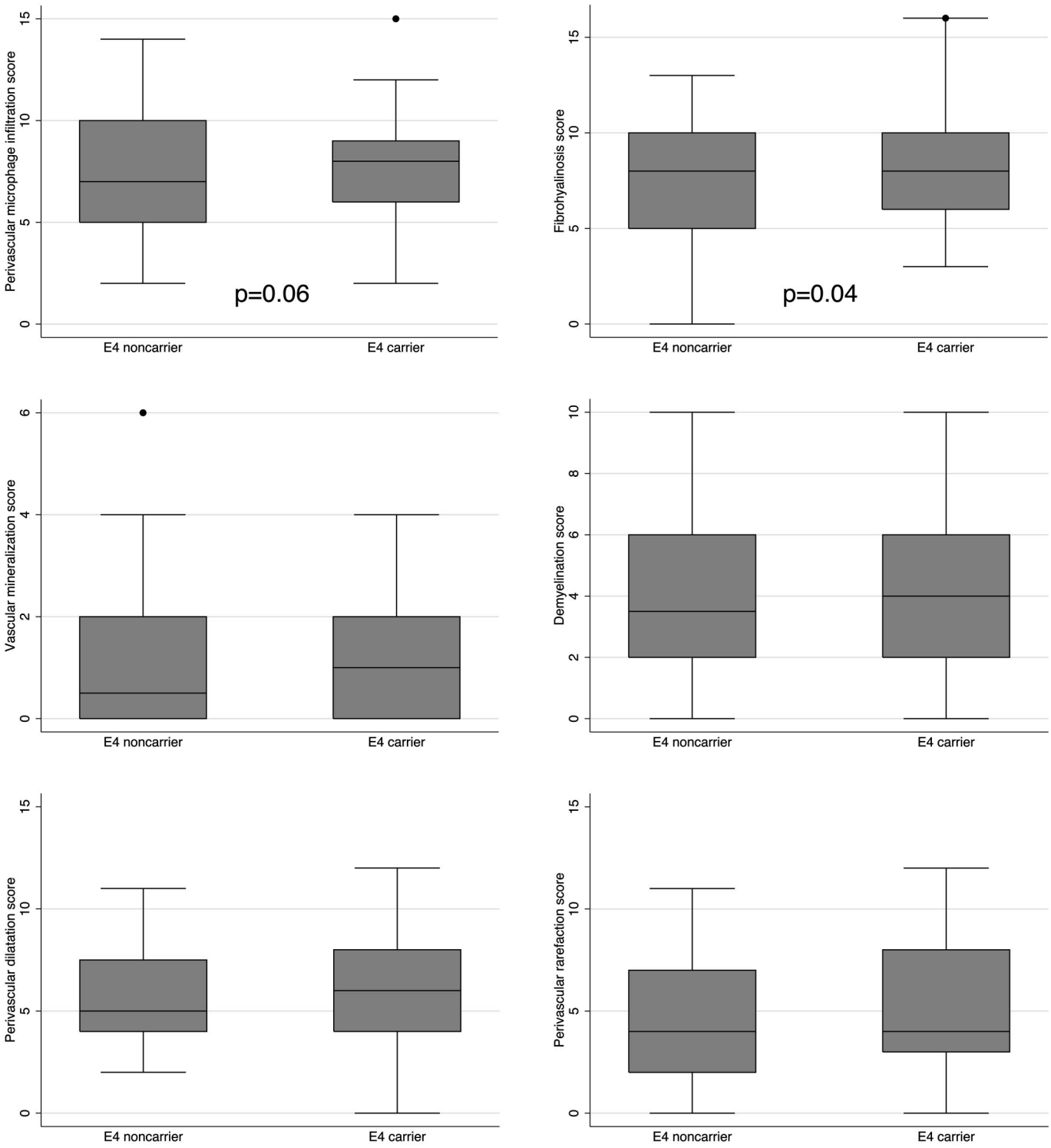

Figure 1. Distribution of fibrohyalinosis/arteriolosclerosis and small vessel disease component measures, by APOE-ε4 status. Box-and-whiskers plots: the box is defined by the 25th centile, median, and 75th centile; the whiskers extend up to 1.5x the interquartile range; dots are outliers.

arteriolosclerosis by some investigators.[30] The sequence of arteriolosclerotic change appears to commence in the basal ganglia and deep white matter, expand into the leptomeninges, thalamus, and cerebellum, and finally progress to involve small vessels of the brainstem.[30] Our finding of an association between *APOE* ε4 and ε2 indicators of arteriolosclerotic severity, namely thickness of the vascular wall and perivascular macrophage infiltration, is unique. Recently, the severity of AD was correlated with more widespread distribution of arteriolosclerotic vessels throughout the brain, although the severity of the arteriolosclerosis lesions was not analyzed.[30]

Cerebral amyloid angiopathy (CAA), the deposi-

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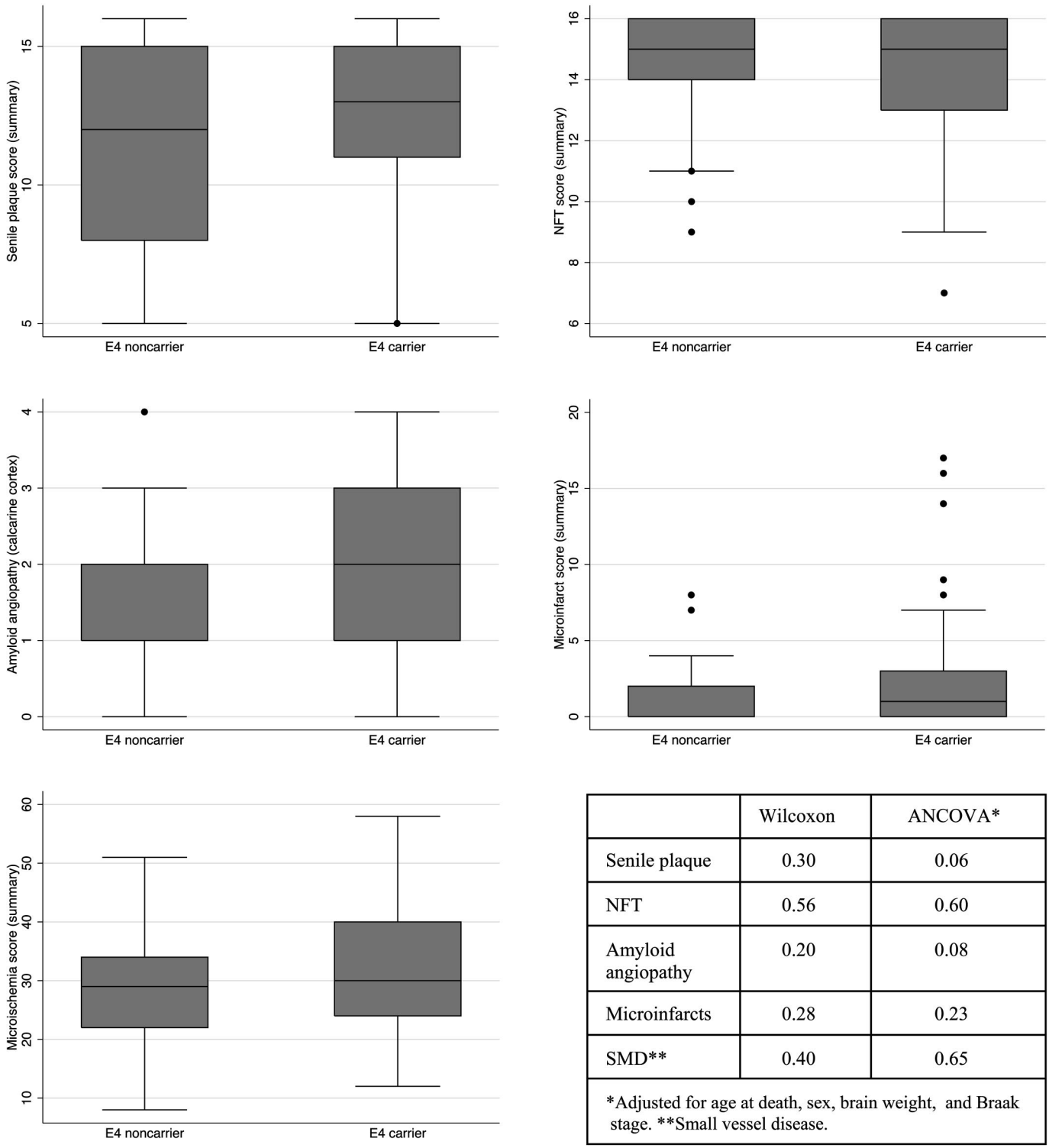

	Wilcoxon	ANCOVA*
Senile plaque	0.30	0.06
NFT	0.56	0.60
Amyloid angiopathy	0.20	0.08
Microinfarcts	0.28	0.23
SMD**	0.40	0.65

*Adjusted for age at death, sex, brain weight, and Braak stage. **Small vessel disease.

Figure 2. Distribution of selected neuropathologic variables, by APOE-ε4 status. See figure 1 for description of the box-and-whiskers plots.

tion of amyloid-beta (Aβ) in the walls of small and medium-sized vessels of the cerebral cortex and leptomeninges, is a common feature of AD brains and appears to be an independent contributor to the dementing process. In the Honolulu Asia Aging Study, cognition scores (adjusted for age, education, *APOE* genotype, and SP and NFT counts) were significantly lower in AD patients whose brains demonstrated CAA at postmortem than in those without CAA.[31] Data from transgenic mouse models indicate that vascular and parenchymal amyloid may have a common neuronal origin, that vascular amyloid is the result of abnormal drainage of parenchymal Aβ, and that virtually identical amyloid-associated pathologies develop as a consequence of parenchymal amyloid and perivascular amyloid.[32,33] These suggest that

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Table 2 *Spearman rank correlation among selected neuropathologic variables*

	Neurofibrillary tangle (NFT)	Neuritic plaque (NP)	Amyloid angiopathy (AA)	Microinfarct (MI)	Small vessel pathology
NFT	1	0.57*	−0.06	−0.11	−0.09
NP		1	−0.05	−0.12	−0.06
AA			1	0.08	−0.008
MI				1	0.25†

* $p<0.0001$; †$p=0.01$.

CAA may be a direct cause of dementia. Alternatively, CAA may indirectly affect cognition by impairing cerebral perfusion, leading to infarction or diffuse ischemic injury.[34,35]

There are few neuropathologic studies investigating the association between *APOE* genotype and small vessel disease. Historically, analyses had been principally limited to cerebral amyloid angiopathy as an outcome.[36-38] The severity of cerebral amyloid angiopathy has been correlated with *APOE*-ε4 repeatedly,[31,36,38] as we observed in our own series. To our knowledge, ours is the first systematic neuropathologic examination between *APOE* genotype and small vessel disease in AD.

Our finding of an association between ε4 and small vessel injury is supported by several recent imaging studies correlating white matter lesions with *APOE* genotype.[39,40] In a study of 1,077 nondemented participants in the Rotterdam scan study, higher Aβ levels were associated with more white matter lesions on MRI among those who were ε4 (+). An associated study found that individuals who were ε4 (+) had significantly higher white matter lesion volume on MRI than those who were ε4 (−) irrespective of the presence or absence of hypertension.[40]

The finding of MRI white matter signal hyperintensities in ε4 (+) individuals suggests an association between ε4 status and small vessel disease, as in our study. The reasons why we did not find a direct correlation between histologic evidence for myelin loss and ε4 status may be methodologic, as white matter changes are amplified by MRI techniques, whereas they are usually less perceptible pathologically.

We found an association between *APOE* genotype and neuritic senile plaque burden in key regions that is consistent with prior reports.[41-44] However, no association was observed with neurofibrillary tangle score. This could be accounted for by the homogeneity of NFT scores in our sample. It has been shown that the association between ε4 status and NFT score varied by age and sex,[44] a finding that cannot be replicated in our demographically restricted sample. We cannot, therefore, rule out an association between ε4 status and NFT burden.

This study has several design strengths. Our sample consists of brain tissue from a cohort of subjects with clearly defined dementia status, clinical course, and high rates of participation in the brain donation program, and relatively homogeneous distribution of such potential confounders as age, sex, education, and ethnicity. Furthermore, a precisely characterized protocol for documenting microvascular pathology in AD brains was followed, and one experienced neuropathologist who was blind to genetic and clinical data performed all examinations, thus eliminating inter-rater variability.

Our results should be interpreted with caution. The composition of the sample limits generalizability of our results to men. Also, because the patients are mostly referred from specialty memory clinics, there may be a bias toward capturing pure cases of AD who will, after death, exhibit neuropathologic findings that are rather exclusive for AD. This may well explain the relative paucity of vascular pathology in the sample. Cross-sectional neuropathologic studies like ours can only suggest associations, not establish causal sequences.

This study is exploratory, and we examined a large number of correlated variables for association with *APOE* genotype without adjustment for the multiple testing. Thus, spurious significant associations could have arisen in this multiple testing situation. It is important that our findings be replicated in independent samples from other brain banks and longitudinal studies. Our analyses considered the effect of *APOE*-ε4 as dichotomous trait. We also evaluated *APOE*-ε4 dose effects models but obtained equivocal results because the power was too low. This issue could be explored more powerfully in a larger brain registry such as the one maintained by the National Alzheimer Coordinating Center.

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