

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*- $\epsilon 4$ vs those who did not. Pairwise rank-order correlations between measures were calculated. The association between *APOE* $\epsilon 4$ status and measures of vascular and AD pathology, adjusting for age at death, sex, brain weight, and Braak stage, were evaluated. **Results:** *APOE*- $\epsilon 4$ was not associated with gross cerebrovascular pathology. Compared to those who were negative, brains from $\epsilon 4$ 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 $\epsilon 4$ ($p = 0.009$), whereas cortical and subcortical microinfarcts were not. There was a trend toward association between *APOE* genotype and amyloid angiopathy ($p = 0.08$), and $\epsilon 4$ was associated with neuritic SP burden, but not NFT. **Conclusion:** *APOE*- $\epsilon 4$ 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 $\epsilon 4$ in some of the microvascular changes commonly found in AD and are consistent with a potential amyloidogenic role for $\epsilon 4$.

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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 $\epsilon 4$ 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) pro-

cessing⁶; β -amyloid protein synthesis,⁷ binding,^{8,9} aggregation,¹⁰ deposition, and clearance^{11,12}; tau phosphorylation¹³; and lipid handling⁶ have been suggested in the neurobiologic literature.

APOE also plays an important role in lipoprotein metabolism—specifically, the functional effects of the $\epsilon 2/\epsilon 3/\epsilon 4$ 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, $\epsilon 4$ is associated with increased risk for cardiovascular disease,¹⁴ ischemic¹⁵ and hemorrhagic¹⁶ 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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