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APOE and Cerebral Amyloid Angiopathy in Community Dwelling Older Persons

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Abstract

Both cerebral amyloid angiopathy and Alzheimer's disease pathology involve abnormal β-amyloid processing. We aim to elucidate the relationship of the apolipoprotein E (*APOE*) genotypes with amyloid angiopathy in the presence of variable amounts of Alzheimer's pathology. Data came from 1,062 autopsied subjects from two community-based studies of aging. Common neuropathologies including Alzheimer's disease and amyloid angiopathy were assessed using uniform methods. *APOE* was genotyped by sequencing the two polymorphisms in codons 112 and 158 of exon 4. We examined the associations of *APOE* with amyloid angiopathy using ordinal logistic regression analyses, controlling for demographics and subsequently Alzheimer's and other common pathologies. Moderate to severe amyloid angiopathy was identified in 35.2% (n=374) of the subjects. 15.3% (n=162) of the subjects were *APOE* ε2 carriers and 26.1% (n=277) ε4 carriers. Adjusting for demographics, the presence of ε4 allele, but not ε2, was associated with more severe

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amyloid angiopathy. After further adjustment for Alzheimer's pathology, both ε2 (odds ratio 1.707, 95% confidence interval 1.236–2.358, p=0.001) and ε4 (odds ratio 2.284, 95% confidence interval 1.730–3.014, p<0.001) were independently associated with amyloid angiopathy. The results were confirmed by path analysis. Further, *APOE* ε4 carriers, but not ε2 carriers, were more likely to have capillary amyloid angiopathy. Accounting for capillary involvement did not alter the *APOE* associations with amyloid angiopathy. We conclude that both *APOE* ε2 and ε4 alleles are associated with more severe cerebral amyloid angiopathy, and the direct effect of ε2 is masked by the allele's negative association with comorbid Alzheimer's pathology. *APOE* ε4, but not ε2, is associated with capillary amyloid angiopathy.

Keywords

APOE; cerebral amyloid angiopathy; capillaries; Alzheimer's disease

Introduction

A prominent feature of cerebral amyloid angiopathy (CAA) is the mural deposition of β-amyloid in the walls of cerebral arteries and arterioles (Greenberg and Vonsattel, 1997). The prevalence of CAA increases with age and is commonly present in persons with Alzheimer's disease (AD) pathology (Love, et al., 2009). CAA is associated with a spectrum of neurological disorders including lobar intracerebral hemorrhage (ICH) and more debatably, ischemic infarction (Arvanitakis, et al., 2011b, Auriel and Greenberg, 2012, Cadavid, et al., 2000, Samarasekera, et al., 2012).

The genetics of sporadic CAA is largely unexplored; however, its pathophysiology suggests that mutations implicated in dysfunctional β-amyloid processing may play a role (Obici, et al., 2005). The apolipoprotein E (*APOE*) gene is a known risk gene for late-onset AD (Roses and Saunders, 1994). The *APOE* isoforms differentially regulate the concentration and clearance of β-amyloid, such that brain amyloid deposition follows an isoform-dependent pattern (*APOE4>APOE3>APOE2*) (Arold, et al., 2012, Castellano, et al., 2011, Holtzman, et al., 2000). As a result, the *APOE* ε4 allele markedly increases the risk of AD while the ε2 allele is protective against the disease relative to the reference ε3 allele. A recent heritability study estimates that the *APOE* locus contributes to 15% of ICH risk variance, and the heritability is driven by lobar ICH predominantly attributable to CAA (Devan, et al., 2013). Indeed, prior literature shows that the *APOE* ε4 allele is associated with a higher risk of CAA (Greenberg, et al., 1995, Premkumar, et al., 1996), suggesting that CAA and AD may share a common biological mechanism such that *APOE* ε4 increases β-amyloid deposition in both brain and cerebral blood vessels. However, the association of *APOE* ε2 with CAA-related ICH is discordant with that of AD. The ε2 allele increases the risk for lobar ICH and the association is stronger in cases with probable or definite CAA (Biffi, et al., 2010, Tzourio, et al., 2008, Valant, et al., 2012). *APOE* ε2 carriers with lobar ICH also tend to have larger haematoma volume (Biffi, et al., 2011) and an increased risk for haematoma expansion (Brouwers, et al., 2012). These findings on ε2 suggest that distinct from ε4 which promotes the vascular amyloid deposition, ε2 is implicated in other vasculopathic changes leading to vessel rupture (Greenberg, et al., 1998). Interestingly, an investigation on CAA

burden by *APOE* genotypes shows that, compared with ε3/ε3, ε2 carriers have more severe CAA, and parenchymal CAA in particular (Nelson, et al., 2013). However, the relationship of ε2 with CAA is not clear as the association was not replicated in a more recent study using data from the National Alzheimer's Coordinating Center (NACC) autopsied subjects (Serrano-Pozo, et al., 2015). Notably, the latter is based on the clinical cohorts for AD, which may result in a disproportional distribution of *APOE* genotypes such as over-representation of ε4.

In this study, utilizing data from more than 1,000 autopsied subjects from the community, we investigated the relationship of the *APOE* genotypes and CAA in the presence of variable amounts of AD pathology. First, we examined the association of the *APOE* genotypes with a semi-quantitative measure of CAA, adjusted for demographics and subsequently for AD and other pathologies. Since earlier literature suggests that amyloid deposition into capillary walls may represent a distinct morphological type (Thal, et al., 2002), we also examined the association of *APOE* and CAA by capillary involvement. Next, we tested the hypothesis that there are two pathways that link the *APOE* genotypes to CAA; a direct pathway and an indirect pathway through AD pathology. The hypothesis for the indirect pathway is supported by findings from transgenic mice models that perivascular drainage pathways, rather than local production or blood uptake, are the mechanism underlying amyloid deposition in CAA, and that β-amyloid of neuronal origin is sufficient to cause cerebral neurodegeneration including CAA (Calhoun, et al., 1999, Carare, et al., 2008, Herzig, et al., 2004, Van Dorpe, et al., 2000).

Material and methods

Study cases

Brains are donated by the individuals from two ongoing clinical pathologic studies of aging, the Religious Orders Study and the Rush Memory and Aging Project (Bennett, et al., 2012a, Bennett, et al., 2012b). Participants enroll without known dementia, and agree to annual clinical evaluations and brain donation after death. Both studies are approved by the Institutional Review Board of the Rush University Medical Center. An informed consent and an anatomical gift act are obtained from each participant.

At the time of the analysis, 3,069 participants had enrolled and 1,429 had died. Of the deceased, 1,232 had undergone autopsy (86%). Neuropathologic diagnosis had been completed for 1,188 autopsied subjects. We restricted to those with complete clinical, genotypic and pathologic information (N=1,083) and further excluded 21 with non-AD dementia. This leaves a total of 1,062 subjects included in the primary analysis. The average age at death was 88.7 years (standard deviation (SD) =6.6, range=65.9–108.3) and the average years of education was 16.3 (SD=3.6, range=3–30). 687 (64.7%) were females.

Neuropathologic assessment

Brain autopsy follows a standard protocol, as previously described (Bennett, et al., 2006b). The brain was removed, weighed, and cut into 1cm slabs. One hemisphere was frozen and the other was fixed in paraformaldehyde for further dissection.

Blocks of tissue from pre-determined brain regions were embedded in paraffin, and then cut and stained for diagnostic assessment by the neuropathologist, blinded to all clinical data. CAA was assessed in four neocortical regions: midfrontal, midtemporal, angular and calcarine cortices. Three monoclonal anti-human β-amyloid antibodies with the following dilutions were used: 1) 6F/3D (1:50, Dako North America Inc., Carpinteria, CA), 2) 10D5 (1:600, Elan Pharmaceuticals, San Francisco, CA) and 3) 4G8 (1:9000, Covance Labs, Madison, WI). We extended a previously published methodology for CAA assessment (Deramecourt, et al., 2012), and a similar protocol is proposed in a recent publication (Love, et al., 2014). Specifically, for each region, meningeal and parenchymal vessels were assessed separately and scored for β-amyloid deposition. Each score was from 0 to 4, where 0=no deposition, 1= scattered segmental but no circumferential deposition, 2=circumferential deposition in up to 10 vessels, 3= circumferential deposition in up to 75% of vessels in the region, and 4=circumferential deposition in over 75% of vessels in the total region. The maximum between the meningeal and parenchymal CAA scores defined the CAA score for that region. If over 50% of the meninges were missing from the section then the cortical region was used to define the score for that region. The scores were averaged across the 4 regions for each case. At least 2 regions must be available for a score to be calculated. The average score was further classified into a 4-level semi-quantitative measure, rated as none, mild, moderate and severe, using consistent cut-offs selected by the neuropathologist. A separate binary measure (present versus absent) was used to assess capillary CAA in any of the four cortical regions. Both CAA measures show moderate to substantial inter-rater agreement. The weighted κ coefficient for the primary CAA measure was 0.47 and the κ coefficient for the binary capillary CAA measure was 0.65.

Counts of neuritic plaque, diffuse plaque and neurofibrillary tangles were measured in midfrontal, superior temporal, inferior parietal, entorhinal cortices, and hippocampus using the Bielschowsky silver stain (Bennett, et al., 2006b). Raw counts of each index were scaled within each region and then averaged across the 5 regions. A composite score for overall burden of AD pathology was used in the analysis by averaging the scaled scores of the three indices. The measure was square root transformed in order to reduce skewness. Separately, Pathologic AD diagnosis followed the National Institute on Aging (NIA) Reagan criteria (Bennett, et al., 2006a). Macroscopic infarcts, microinfarcts and Lewy bodies were identified as described previously (Arvanitakis, et al., 2011a, Schneider, et al., 2012).

APOE genotyping

DNA was extracted from peripheral blood mononuclear cells, and in some cases DNA from frozen post-mortem brain tissue (cerebellum) was used. The *APOE* genotypes were determined by sequencing codon 112 (position 3937) and codon 158 (position 4075) in exon 4 (Boyle, et al., 2010). Cases with 1 or more copies of ε4 allele were considered ε4 carriers, and cases with 1 or more copies of ε2 allele were considered ε2 carriers.

Statistical analysis

Chi-square tests and Spearman correlations were used to examine the bivariate relationships of CAA with AD and other neuropathologic indices, as well as the *APOE* genotypes. Analysis of variance was used to examine the relationship of *APOE* with age at death.

Ordinal logistic regression models tested the associations of the *APOE* genotypes with the odds of having more severe CAA. In the primary models, the semi-quantitative measure of CAA was the ordinal outcome, and the models included a term for *APOE* ε4 carriers and a separate term for ε2 carriers. The corresponding regression coefficients estimated the log odds ratios (ORs) of having more severe CAA among *APOE* ε4 (or ε2) carriers relative to the reference group (*APOE* ε3/3 carriers). We adjusted for age, sex and education in the initial analysis, and in subsequent models we further adjusted for a composite measure of AD pathology, as well as the presence of macroscopic infarcts, microinfarcts, and Lewy bodies. Secondary analysis included examination of the association of *APOE* with the presence of capillary CAA. We also investigated the dosage effect of the *APOE* genotypes. We then performed stratified analysis to examine whether the association of *APOE* with CAA differed in groups with and without capillary involvement.

Considering that the *APOE* gene is implicated in AD pathology and CAA commonly coexisted with AD, we hypothesized that the relationship between the *APOE* genotypes and CAA may involve AD pathology. We tested this hypothesis by conducting path analysis. Path analysis is a special form of structural equation model, where we dissected the total effect of *APOE* genotypes on CAA into two contributing pathways, that is a direct effect and an indirect effect through AD pathology. The pathway diagram is presented in Figure 3.

The analyses were conducted using SAS/STAT software, version 9.3 (SAS Institute Inc. Cary, NC, USA) and Mplus 7.11 (Muthen & Muthen). A nominal level of α=0.05 was used to determine statistical significance.

Results

Amyloid angiopathy, AD and other common neuropathologies

The pathologic characteristics of the study group are presented in Table 1. Briefly, more than a third (N=374) had moderate to severe meningeal/parenchymal CAA, and 16% (N=170) had capillary CAA. As would be expected, the two measures were highly correlated such that the capillary involvement was associated with more severe meningeal/parenchymal CAA (p<0.001). About 18% of the subjects with capillary CAA (N=31) had mild CAA in meningeal/parenchymal vessels.

A pathologic diagnosis of AD was made in 63% (N=672) of the subjects. The association between meningeal/parenchymal CAA and pathologic AD diagnosis was highly significant (p<0.001). 44.4% (N=298) of the subjects with pathologic AD diagnosis having moderate to severe CAA. By contrast, of the 390 subjects without pathologic AD, only 19.5% (N=76) had moderate to severe CAA. A similar association was observed between CAA and the composite measure of AD pathology (Spearman correlation coefficient=0.38, p<0.001). Notably, approximately 80% of all subjects with moderate to severe CAA had pathologic diagnosis of AD. Bivariate analyses did not show association of meningeal/parenchymal CAA with the presence of macroscopic infarcts (p=0.589), microinfarcts (p=0.143) or Lewy bodies (p=0.711).

The presence of capillary CAA was also strongly associated with pathologic AD ($p<0.001$). 20.7% (N=139) of subjects with pathologic diagnosis of AD had presence of capillary CAA, and the percentage was 8.0% (N=31) for those without pathologic AD diagnosis. Similar to meningeal/parenchymal CAA, a majority (> 80%) of the subjects with capillary CAA had pathologic AD. Bivariate analyses showed that capillary CAA was significantly associated with Lewy bodies ($p=0.021$), but not with macroscopic infarcts ($p=0.587$) or microinfarcts ($p=0.056$). Notably, after adjustment for AD pathology, the presence of Lewy bodies was no longer associated with capillary CAA ($p=0.142$).

Amyloid angiopathy and *APOE* genotypes

A majority (60.6%) of the subjects had *APOE* ε3/ε3 genotype, 15.3% were *APOE* ε2 carriers, and 26.1% were ε4 carriers. The mean age for the subjects with ε3/3 genotype was 88.9 years (SD=6.7). Comparing with ε3/3 carriers, ε4 carriers were on average 1 year younger at the time of death ($p=0.017$). We did not find significant age difference between ε3/3 carriers and ε2 carriers ($p=0.196$). In a series of logistic regression analyses, we examined associations of the *APOE* genotypes with pathologic indices of macroscopic infarcts, microinfarcts and Lewy bodies. Although we and others have previously reported associations of *APOE* ε4 with cerebral infarction and Lewy bodies (Schneider, et al., 2005, Tsuang, et al., 2013, Yu, et al., 2014), in this study we failed to replicate these associations after adjustment for demographics and AD pathology (data not shown).

Next, we examined the association of *APOE* with meningeal/parenchymal CAA. Figure 1 shows representative CAA localization by the *APOE* genotypes. A subject with ε3/3 genotype shows sparse CAA which is confined to segmental deposition of β amyloid in only meningeal vessels, and the cortex shows few β amyloid plaques. Separately, a ε2 carrier shows CAA in meningeal and intracerebral cortical vessels but few β amyloid plaques. In contrast, a ε4 carrier shows marked CAA in meningeal and intracerebral cortical vessels as well as frequent β amyloid plaques in the cortex. 27.5% of the subjects with ε3/3 genotype had moderate to severe meningeal/parenchymal CAA, and the percentage increased to 37.0% and 55.2% respectively for the ε2 and ε4 carriers. This isoform-dependent pattern is illustrated in Figure 2C. As contrast, comparing with ε3/3 carriers, ε4 carriers had more AD pathology and ε2 carriers had less AD pathology. In particular, 59.9% of the ε3/3 carriers, 48.8% of the ε2 carriers, and 80.5% of the ε4 carriers had pathologic AD diagnosis (Figure 2D).

In an ordinal logistic regression model adjusted for age, sex and education, the odds of having more severe meningeal/parenchymal CAA was tripled for *APOE* ε4 carriers (OR=3.554, 95% CI=2.728–4.630, $p<0.001$) relative to the ε3/3 reference group. In the same model, we did not find a significant association of *APOE* ε2 with CAA (OR=1.212, 95% CI=0.887–1.658, $p=0.228$). However, after we augmented the model by adding a term for the composite measure of AD pathology, both ε4 (OR =2.284, 95% CI =1.730–3.014, $p<0.001$) and ε2 (OR=1.707, 95% CI =1.236–2.358, $p=0.001$) were independently associated with more severe CAA. These associations persisted after further adjustment for cerebral infarcts and Lewy bodies (Table 2). We repeated the analyses to examine the associations of *APOE* with capillary CAA (Table 3). *APOE* ε4 remained strongly associated

with the presence of capillary CAA (OR =4.149, 95% CI =2.835–6.073, $p<0.001$). The association of ε2 was not significant (OR=1.269, 95% CI =0.731–2.203, $p=0.398$).

Next, we investigated the dosage effect of the *APOE* genotypes and the results were consistent. In the model adjusted for demographics, AD, infarcts and Lewy bodies pathologies, each additional copy of ε4 allele increased the odds of more severe meningeal/parenchymal CAA 2.5 fold (OR =2.507, 95% CI =1.939–3.243, $p<0.001$), and each additional copy of ε2 allele increased the odds of more severe CAA over 1.5 fold (OR =1.685, 95% CI =1.244–2.284, $p<0.001$).

Amyloid angiopathy and *APOE* genotypes by capillary involvement

A previous study (Thal, et al., 2002) suggests that the association of *APOE* genotypes with CAA may differ depending on the capillary involvement. Therefore, we examined the *APOE* association with CAA separately in groups with and without capillary involvement (Table 4). In the larger group of subjects without capillary CAA, relative to the ε3/3 reference group, both ε4 (OR=1.636, 95% CI =1.179–2.269, $p=0.003$) and ε2 carriers (OR=1.566, 95% CI =1.103–2.223, $p=0.012$) showed greater odds for more severe CAA. Similar associations were found in the smaller group of subjects with capillary involvement.

APOE ε2 and amyloid angiopathy association is masked by AD

The logistic regression analysis suggests that the overall association of *APOE* ε2 with CAA may be masked by comorbid AD pathology. To examine this potential masking, we conducted a path analysis and dissected the total effect of *APOE* genotypes on CAA into direct and indirect effects through AD pathology. For the indirect pathway we placed AD upstream of CAA because recent data from animal models suggests that perivascular drainage of neuronal amyloid may be one mechanism for the development of CAA. The decision was also supported by our data that a predominant majority of subjects with CAA had pathologic AD (80%), while only less than half of those with pathologic AD had CAA (44%). The path coefficients and standard errors (SEs) for each pathway are illustrated in Figure 3. Similar to the logistic regression models, these path coefficients compare the log-odds of having more severe CAA between *APOE* genotypes.

In this analysis, the direct and indirect effects of both ε4 and ε2 genotypes were significant. We focused on *APOE* ε2. Consistent with the result from the logistic regression model, the direct link between ε2 and CAA had an OR of 1.733 ($p=0.002$), suggesting ε2 carriers had a higher risk for more severe CAA than ε3/3 carriers. Separately, we found that *APOE* ε2 was associated with less AD pathology, and AD pathology was associated with greater odds of more severe CAA. The indirect effect of ε2 on CAA through AD was in the opposite direction (OR =0.730, $p<.0001$). As the result, without disentangling the association with AD pathology, the total effect of ε2 on CAA was masked and not significant ($p=0.196$).

We repeated the path analysis by the presence of capillary CAA. The result for subjects without capillary CAA was similar and the masking was evident. The path coefficient that links ε2 to CAA was significant such that ε2 carriers had a higher risk for more severe CAA (OR=1.590, $p=0.012$), which was coupled with a negative association of ε2 with less AD

pathology. We did not find the masking in subjects with capillary CAA, however the direct effect of ε2 on CAA remained significant (OR=4.380, *p*=0.007).

Finally, the percentages of moderate to severe CAA by *APOE* genotypes differed by the burden of AD pathology. In subjects with pathologic AD diagnosis, 34.5% of the ε3/3 carriers had moderate to severe CAA; this increased to 50.6% and 61.4% for the ε2 and ε 4 carriers, respectively. As contrast, in subjects without pathologic AD diagnosis, only 17.1% of the ε3/3 carrier had moderate to severe CAA, and the percentage increased to 24.1% and 29.6% for the ε2 and ε4 carriers, respectively. To test the hypothesis that the association of *APOE* genotypes with CAA may differ by AD pathology, we added ε2 by AD and ε4 by AD interactions to the ordinal logistic regression model. Indeed, both genotypes showed stronger associations with more severe CAA in the presence of more AD pathology. Adjusting for demographics, infarcts, and Lewy bodies, the odds ratio of having more severe CAA for the *APOE* ε2 by AD pathology interaction was 3.000 (95% CI 1.167–7.712, *p*=0.023), and the odds ratio for the ε4 by AD pathology interaction was 2.160 (95% CI 1.048–4.449, *p*=0.037).

Discussion

In this study, we show that both *APOE* ε2 and ε4 genotypes are associated with more severe CAA and the associations are independent of AD and other neuropathologies that are common in aging brain. We observe that *APOE* ε4, but not ε2, is associated with presence of capillary CAA. Accounting for capillary involvement did not alter the *APOE* associations with CAA.

The relation of *APOE* to CAA and CAA-related ICH has been previously reported. Earlier studies suggest that the ε2 and ε4 genotypes are related to ICH through different mechanisms, such that the ε4 allele promotes vascular amyloid accumulation while ε2 contributes to vessel rupture via other vasculopathic changes such as fibrinoid necrosis (Greenberg, et al., 1998, McCarron and Nicoll, 2000, McCarron, et al., 1999). Interestingly, there is new evidence that ε2 carriers have more severe CAA, suggesting a direct involvement of ε2 in accumulation of β-amyloid in cerebral vasculature. However, the association of *APOE* ε2 with CAA remains unclear, likely due to fewer cases with the ε2 genotype (Rannikmae, et al., 2014) or the data which reply on clinical cohorts. Using data from over 1,000 well characterized older persons, we confirm the direct association of ε2 with CAA.

The neuropathology of AD and CAA involve abnormal accumulation and clearance of β-amyloid; however, it is unclear whether the deposition of β-amyloid in the vessel wall has a neuronal origin. Three mechanistic hypotheses have been proposed with regards to cerebral amyloid deposition (Burgermeister, et al., 2000). First, the vessel wall theory hypothesizes that β-amyloid is produced and deposited locally by vascular smooth muscle cells. Second, the blood uptake theory suggests that circulating amyloid beta peptide binds to the receptor for advanced glycation end-products (RAGE) in endothelial cells and is transported through the blood-brain barrier into brain (Deane, et al., 2003). Third, the perivascular drainage theory suggests that amyloid originates from the central nervous system (CNS) and drains

out of brain along perivascular spaces (Weller, et al., 1998, Weller, et al., 2008). Experiments using transgenic mice show that neuronal overexpression of mutant APP results in significant cerebral amyloid deposition (Calhoun, et al., 1999, Herzig, et al., 2004). In our data, 80% of the brains with moderate to severe CAA met pathologic AD criteria, and less than half of pathologic AD brain had moderate to severe CAA. Such asymmetric pattern is even more evident in the case of capillary CAA, where over 80% of the subjects with capillary CAA had pathologic diagnosis of AD, and only 21% of ADs had capillary CAA. These results are in support of the drainage pathway hypothesis.

The isoform dependent pattern of *APOE* in the clearance of brain amyloid makes it no surprise that the *APOE* ε4 allele was associated with more severe CAA (Alonzo, et al., 1998, Olichney, et al., 1996, Premkumar, et al., 1996). Yet the *APOE* ε2 results are interesting. Our data support that the ε2 allele was associated with less AD pathology; and after controlling for AD pathology, the allele was associated with more severe CAA. Separately, there is evidence that the association of *APOE* with CAA was stronger in persons with more AD pathology. These findings suggest that the role of *APOE* ε2 in the pathologic process of AD may be distinct from that of CAA. A biochemical study shows that the Aβ42: Aβ40 ratio differs between vascular and plaque amyloid such that amyloid in vessel walls is predominantly Aβ40 while Aβ42 is more abundant in cortical plaques (Van Dorpe, et al., 2000). A high Aβ40:Aβ42 ratio favors vascular amyloidosis and increase in the Aβ40:Aβ42 ratio may shift the amyloid deposition from parenchyma to vasculature (Herzig, et al., 2006). Immunotherapy studies also suggest that selective clearance of Aβ42 reduces the parenchymal amyloid deposition, but it induces vascular amyloid deposition (Herzig, et al., 2004). Further investigation on whether *APOE* ε2 contributes preferentially to Aβ42 clearance is warranted.

Multiple processes may be involved in amyloid deposition in CAA. One study on 41 postmortem brains with CAA shows that, depending on whether or not the disease involves cortical capillaries, there are two distinct morphological types of CAA; where cases with amyloid deposition in capillaries have higher ε4 allele frequency and those without capillaries deposition have higher ε2 allele frequency (Thal, et al., 2002). The study proposed that the amyloid deposition in capillaries shares a similar mechanism with amyloid plaques in cortices, for which the ε4 allele is a known risk factor. On the other hand, the ε2 allele promotes amyloid deposition that involves arterioles. We showed that *APOE* ε4 was also associated with the presence of capillary CAA but the association of *APOE* ε2 with capillary CAA didn't reach statistical significance, which supports the previous study. On the other hand, we found that the ε2 and CAA association persisted regardless of capillary involvement.

The study has strengths and weaknesses. To our knowledge, this is by far the largest community based study that examines postmortem human brain for association of the *APOE* genotypes with CAA. Brains are collected from two longitudinal clinicopathologic cohort studies, which have very high follow-up and autopsy rates. Uniform clinical and pathologic evaluation protocols are applied in both studies by the same group of investigators, which makes it efficient to merge the data for combined analysis. One limitation is that lack of information on CAA related hemorrhages prevents us from further clarifying the

relationship of *APOE* with CAA and the downstream effect on ICH. The quantification and classification of hemorrhages is currently not available in these cohorts. Separately, the study participants are older and have higher education comparing with the general population. Our findings await independent replications from other prospective studies.

Conclusions

We investigated the relationship of the *APOE* genotypes, CAA, and AD pathology utilizing genetic and neuropathologic data from over 1000 post-mortem human brains. We found that the *APOE* ε4 and ε2 alleles were both associated with more severe meningeal/parenchymal CAA, and that the association of ε2 with CAA was initially masked by comorbid AD pathology. *APOE* ε4, but not ε2, was associated with capillary CAA. Further, the associations of the *APOE* genotypes with CAA were significant with or without capillary involvement.

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Abbreviations

CAA	cerebral amyloid angiopathy
AD	Alzheimer's disease
ICH	intracerebral hemorrhage
SD	standard deviation
OR	odds ratio
SE	standard error
CI	confidence interval
df	degrees of freedom

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- We examined the relationship of the *APOE* genotypes with cerebral amyloid angiopathy in the presence of variable amounts of Alzheimer's pathology using data from over 1000 postmortem brains.
- Both ε2 and ε4 alleles were associated with more severe cerebral amyloid angiopathy.
- *APOE* ε4, but not ε2, was associated with the presence of capillary amyloid angiopathy.
- The *APOE* associations with amyloid angiopathy persisted regardless of capillary involvement.
- The relationship of ε2 with amyloid angiopathy was masked by ε2′s protective association with comorbid Alzheimer's pathology.

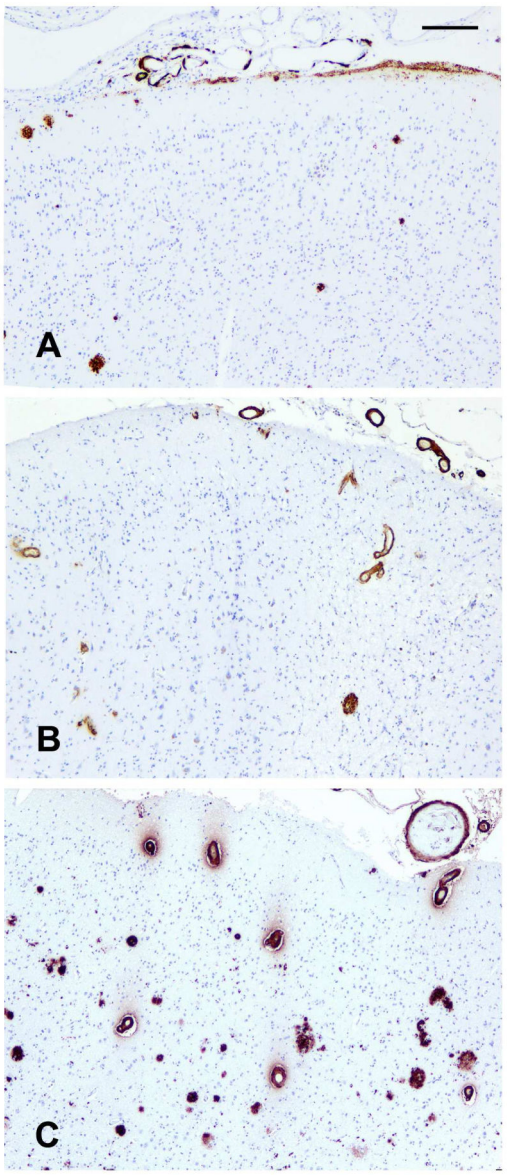

Figure 1.

illustrates representative CAA localization by the *APOE* genotypes. (A) shows a subject with ε3/3 genotype with sparse CAA which is confined to segmental deposition of β amyloid in only meningeal vessels, and the cortex has few β amyloid plaques. (B) shows a ε2 carrier with CAA present in meningeal and intracerebral cortical vessels, as well as few β amyloid plaques in the cortex. (C) shows a ε4 carrier with marked CAA in meningeal and intracerebral cortical vessels, as well as frequent β amyloid plaques in the cortex. Scale bar = 150 μm.

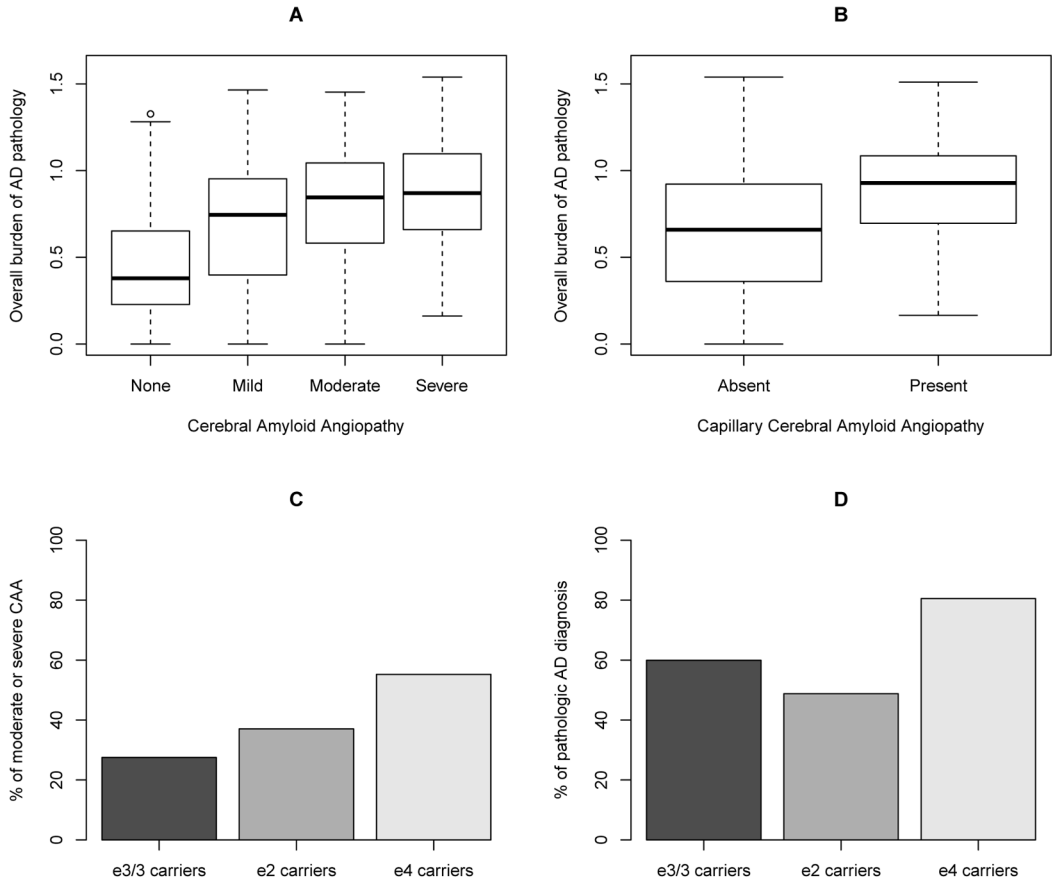

Figure 2.

illustrates relationship of AD pathology, CAA and *APOE* genotypes. (A) and (B) show the distribution of the composite measure of AD pathology by CAA. The association of CAA with more burden of AD pathology is evident. (C) shows the percentages of moderate to severe CAA by *APOE* genotypes. The figure illustrates isoform-dependent pattern of *APOE* (i.e. ε4>ε2>ε3) in relation to CAA. (D) shows the percentages of pathologic AD diagnosis by *APOE* genotypes. Here, we observe a different pattern in relation to AD (i.e. ε4>ε3>ε2), as compared with CAA (C).

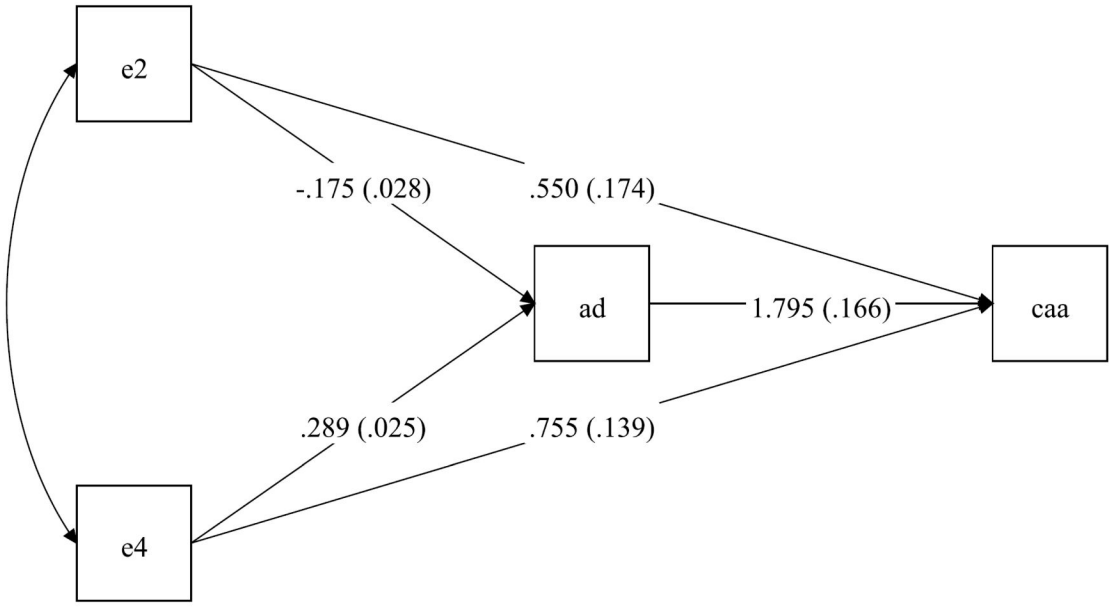

Figure 3.

summarizes the path analysis of *APOE* genotypes and CAA where the model links the presence of *APOE* ε2 allele, and separately ε4 allele, with CAA, either directly or indirectly through an effect on AD pathology. The path coefficients (standard errors) estimate the associations of *APOE* genotypes with AD and subsequently CAA. All the coefficients are significant, and the result reveals that there is a significant direct effect of ε2 on CAA which is masked by the allele's negative association with AD pathology.

Table 1

Descriptive of the study group (N=1,062)

Age at death (mean, SD)	88.7, 6.6
Female Sex (N, %)	687, 64.7%
Education (mean, SD)	16.3, 3.6
Non-Hispanic Whites (N, %)	1014, 95.6%
APOE genotypes (N, %)	
ε2/2	7, 0.7%
ε2/3	134, 12.6%
ε2/4	21, 2.0%
ε3/3	644, 60.6%
ε3/4	240, 22.6%
ε4/4	16, 1.5%
Composite measure of AD pathology (mean, SD)[1]	0.76, 0.40
Pathologic diagnosis of AD by NIA-Reagan criteria (N, %)	672, 63.3%
Macroscopic infarcts (N, %)	368, 34.7%
Microinfarcts (N, %)	304, 28.6%
Lewy Bodies (N, %)	229, 21.6%
Rating of CAA (N, %)	
None	220, 20.7%
Mild	468, 44.1%
Moderate	245, 23.1%
Severe	129, 12.1%
Capillary CAA (N, %)	170, 16.0%

[1] Square root transformed

Table 2

Association of *APOE* with meningeal/parenchymal CAA

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Age at death	1.050 (1.032, 1.069)*	1.033 (1.015, 1.052)*	1.033 (1.014, 1.052)*
Male Sex	1.038 (0.817, 1.320)	1.175 (0.921, 1.500)	1.184 (0.927, 1.511)
Education	0.998 (0.967, 1.029)	1.003 (0.971, 1.035)	1.003 (0.972, 1.036)
AD[1]	-	5.537 (3.970, 7.721)*	5.597 (4.009, 7.814)*
Macroscopic infarcts	-	-	0.926 (0.724, 1.184)
Microinfarcts	-	-	1.210 (0.937, 1.563)
Lewy Bodies	-	-	0.954 (0.725, 1.257)
APOE ε2	1.212 (0.887, 1.658)	1.707 (1.236, 2.358)*	1.709 (1.237, 2.361)*
APOE ε4	3.554 (2.728, 4.630)*	2.284 (1.730, 3.014)*	2.296 (1.739, 3.032)*

[1] Composite measure of AD pathology;

* $p<0.05$;

Model 1 was adjusted for demographics; Model 2 was adjusted for demographics and AD pathology; Model 3 was adjusted for demographics, AD pathology, as well as presence of infarcts and Lewy bodies.

Table 3

Association of *APOE* with capillary CAA

	Model 1 OR (95% CI)	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**
Male Sex	0.902 (0.616, 1.320)	0.989 (0.670, 1.459)	0.986 (0.667, 1.460)
Education	1.045 (0.994, 1.098)	1.055 (1.003, 1.110)*	1.057 (1.004, 1.113)*
AD[1]	-	3.797 (2.247, 6.418)*	3.816 (2.243, 6.494)*
Macroscopic infarcts	-	-	0.936 (0.637, 1.375)
Microinfarcts	-	-	1.534 (1.037, 2.270)*
Lewy Bodies	-	-	1.374 (0.913, 2.067)
APOE ε2	0.966 (0.569, 1.640)	1.250 (0.723, 2.161)	1.269 (0.731, 2.203)
APOE ε4	5.747 (4.018, 8.221)*	4.155 (2.845, 6.066)*	4.149 (2.835, 6.073)*

[1]Composite measure of AD pathology;

*$p<0.05$;

Model 1 is adjusted for demographics; Model 2 adjusted for demographics and AD pathology; Model 3 is adjusted for demographics, AD pathology, as well as presence of infarcts and Lewy bodies;

Table 4

Association of *APOE* with CAA by capillary involvement

	Without capillaries OR (95% CI)	**With capillaries OR (95% CI)**
Age at death	1.028 (1.008, 1.049)*	1.007 (0.951, 1.065)
Male Sex	1.225 (0.936, 1.604)	1.005 (0.523, 1.932)
Education	0.995 (0.961, 1.031)	0.967 (0.891, 1.049)
AD[1]	5.594 (3.881, 8.061)*	1.494 (0.571, 3.910)
Macroscopic infarcts	0.924 (0.703, 1.215)	1.149 (0.611, 2.159)
Microinfarcts	1.133 (0.851, 1.511)	0.896 (0.476, 1.683)
Lewy Bodies	0.843 (0.617, 1.153)	0.947 (0.494, 1.815)
APOE ε2	1.566 (1.103, 2.223)*	4.221 (1.487, 11.982)*
APOE ε4	1.636 (1.179, 2.269)*	1.640 (0.863, 3.115)

[1]Composite measure of AD pathology;

*$p<0.05$.

Both models were adjusted for demographics, AD pathology, as well as presence of infarcts and Lewy bodies;