Clinical Predictors of Severe Cerebral Amyloid Angiopathy and Influence of APOE Genotype in Persons With Pathologically Verified Alzheimer Disease

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IMPORTANCE Although cerebral amyloid angiopathy (CAA) has important clinical implications, our understanding of it and ability to diagnose it are limited.

OBJECTIVE To determine pathological correlates and clinical factors identifiable during life that predict the presence of severe CAA in persons with pathologically confirmed Alzheimer disease (AD).

DESIGN, SETTING, AND PARTICIPANTS We compared demographic and clinical variables at the earliest visit during life at which participants were found to have cognitive impairment and compared pathological variables between persons ultimately found to have no or severe CAA at autopsy using logistic regression. Analyses were repeated separately for carriers and noncarriers of the APOE ε4 allele. Data were obtained from the Uniform Data Set, which comprises longitudinal clinical assessments performed in the Alzheimer’s Disease Centers funded by the National Institute on Aging. Participants included 193 persons with AD and severe CAA and 232 persons with AD and no CAA. All participants had cognitive impairment and met National Institute on Aging-Reagan Institute neuropathological criteria for AD.

MAIN OUTCOMES AND MEASURES Prevalence of demographic characteristics and the APOE ε4 allele and odds ratios (ORs) of clinical variables for the prediction of severe CAA.

RESULTS Persons with severe CAA compared with those without CAA were more likely to carry an APOE ε4 allele (64.9% vs 42.8%, respectively; P < .001), to be Hispanic (6.8% vs 1.3%, respectively; P = .003), to have had a transient ischemic attack (12.5% vs 6.1%, respectively; OR = 2.1; 95% CI, 1.0-4.4), and to have lower degrees of diffuse amyloid plaque pathology (mean [SD] Consortium to Establish a Registry for Alzheimer’s Disease score, 1.2 [0.5] vs 1.4 [0.8], respectively; P = .01). Those with CAA compared with those without CAA more commonly had intracerebral hemorrhage (9.3% vs 3.5%, respectively; P = .01), cortical microinfarcts (20.7% vs 12.9%, respectively; P = .03), and subcortical leukoencephalopathy (20.5% vs 12.1%, respectively; P = .02). Noncarriers of the APOE ε4 allele with severe CAA compared with those without CAA had a higher prevalence of stroke (11.1% vs 3.9%, respectively; OR = 3.8; 95% CI, 1.0-14.6) and hypercholesterolemia (50.0% vs 32.7%, respectively; OR = 2.3; 95% CI, 1.1-4.7).

CONCLUSIONS AND RELEVANCE Being Hispanic and having had a transient ischemic attack–like episode were predictors of CAA in persons with AD. Less diffuse parenchymal amyloid pathology in persons with severe CAA suggests a difference in β-amyloid trafficking.

he prevalence of cerebral amyloid angiopathy (CAA) increases with age, being found in the brain of 36% of individuals older than 60 years and 46% of those older than 70 years. It is more common in persons dying with dementia, being present in 55% to 59%, and occurs in 80% of those with concurrent Alzheimer disease (AD) pathology. In addition to possibly contributing independently to cognitive dysfunction, CAA is associated with an increased risk of spontaneous and anticoagulant-related intracerebral hemorrhage (ICH). It is also associated with a higher risk of vascular complications of antiamyloid therapies being used to treat AD. Although CAA currently remains a diagnosis only made definitively by biopsy or autopsy, its clinical implications during life are increasingly evident.

Current criteria for the diagnosis of definite CAA require demonstration of CAA on postmortem examination. Probable and possible CAA require that a lobar ICH has already occurred. Although microhemorrhages are the most common manifestation of CAA on magnetic resonance imaging, lobar ICHs can be large and have devastating neurological consequences. The risk of such hemorrhages is increased by antiplatelet and anticoagulant medications. The microhemorrhages associated with CAA may be asymptomatic but CAA can also present with transient ischemic attack (TIA)-like events. Although gradient recalled echo and susceptibility-weighted magnetic resonance imaging can sensitively detect microhemorrhages and superficial siderosis of CAA, such magnetic resonance imaging techniques still identify the presence of CAA only after ICH. Amyloid imaging using ligands such as N-methyl-carbon 11-2-(4'-methylamino-phenyl)-6-hydroxybenzothiazole (also known as carbon 11–labeled Pittsburgh Compound B) shows some promise in identifying CAA during life, although it is not currently possible to reliably differentiate between vascular and parenchymal amyloid using this technique.

There is significant variation in the pathological appearance of CAA. Although the reasons underlying interindividual differences are largely unknown, they may at least in part be related to genetic variation. Variation in CRI has been found to be related to CAA and it is evident that polymorphisms in the apolipoprotein E gene (APOE) also play a role. The ε4 allele of APOE is associated with an increased risk for AD as well as for parenchymal and vascular deposition of derivatives of the amyloid precursor protein, especially β-amyloid (Aβ). Persons with the APOE ε4 allele are more likely to develop CAA in capillaries, and persons with the ε2 variant are more likely to have ICH. Cerebral amyloid angiopathy associated with different APOE genotypes may therefore have distinct pathological manifestations and clinical implications.

The aims of this study were the following: (1) to identify clinical factors associated with the presence of severe CAA in persons with AD pathology at the time of autopsy; (2) to assess these associations separately among carriers and noncarriers of the APOE ε4 allele; and (3) to assess whether there are differences in pathological comorbidities occurring in persons with severe CAA relative to those without CAA, collectively and separately for carriers and noncarriers of the APOE ε4 allele. We analyzed demographic and clinical data from the Uniform Data Set (UDS) of the National Institute on Aging (NIA)-funded Alzheimer’s Disease Center (ADC) system in which participants undergo longitudinal comprehensive standardized clinical assessments. A subset of UDS participants ultimately underwent neuropathological examination and had data collected using the Neuropathology Data Set Form.

Methods

The National Alzheimer’s Coordinating Center collects the UDS from the network of NIA-funded ADCs in the United States. Participants and study partners enrolled in the UDS give informed consent (with written and verbal consent procedures varying across ADC sites) and undergo comprehensive clinical and cognitive evaluations annually at one of the ADCs. At each visit, a summary of findings is elaborated and a diagnosis is rendered. A subset of participants was also enrolled in site-specific genetic, imaging, or other biomarker protocols from which APOE genotyping was available. This study includes data entered into the UDS from its inception in 2005 through June 1, 2013. Being a secondary analysis of data acquired under institutional review board review at each institution, institutional review board approval for the current investigation was waived.

The brains of persons undergoing autopsy in the UDS are rated for the degree of CAA present (none, mild, moderate, severe, not assessed, or missing) and undergo semiquantitative assessments of the density of neurofibrillary tangles (Braak score), neuritic and diffuse plaques (Consortium to Establish a Registry for Alzheimer’s Disease [CERAD] criteria; sparse, moderate, or frequent plaques), and cerebrovascular pathology. Cerebrovascular pathology is documented as the following being either present or absent: (1) 1 or more large-artery cerebral infarcts; (2) 1 or more cortical microinfarcts; (3) 1 or more lacunes; (4) single or multiple hemorrhages; and (5) subcortical arteriosclerotic leukoencephalopathy.

Using this database, we identified participants with cognitive impairment during life who met NIA-Reagan Institute criteria for AD at the time of autopsy. For participants with multiple visits, the earliest visit at which they demonstrated cognitive impairment was studied. As there was no systematic effort to standardize grading of CAA across centers, there was the possibility that intermediate severities of CAA (mild and moderate) may not have been differentiated in a common manner. In light of this and the likelihood that CAA is most likely to be clinically relevant when severe, comparisons were made between persons with no CAA and those determined to have severe CAA. Demographic variables were compared between persons with no CAA and severe CAA by χ² tests and t tests as appropriate. These included age at the time of death, sex, education, ethnicity (Hispanic vs non-Hispanic), race, age at which cognitive decline began, and time between onset of cognitive decline and death.

Logistic regression was used to estimate odds ratios (ORs) of clinical variables at the first visit at which the participant had abnormal cognition for predicting the presence of severe CAA at autopsy (see Box for a comprehensive list of variables...
Results

Two hundred thirty-two participants with NIA–Reagan Institute criteria–defined AD and no CAA were compared with 193 participants with AD and severe CAA. The APOE genotype was available for 194 of the 232 persons with no CAA (83.6%) and 165 of the 193 persons with severe CAA (85.5%). The frequency of severe CAA varied significantly with APOE genotype (P < .001) (Table 1). Persons with the APOE ε4/ε4 genotype were more likely to have severe CAA (73.4%) than no CAA (26.6%). A total of 45.7% of persons with the ε3/ε4 genotype had severe CAA relative to 34.2% of those with the ε3/ε3 genotype. The presence of at least 1 copy of the ε4 allele was associated with a higher prevalence of severe CAA relative to no CAA (64.9% vs 42.8%, respectively; P < .001). In this population of persons with pathologically confirmed AD, the frequency of persons with any APOE ε2 allele was low (n = 21 [5.8%]). Therefore, for analyses of effects of the ε4 allele, participants with any ε2 allele were excluded and the remaining participants were dichotomized into those having 1 or 2 ε4 alleles (ie, ε3/ε4 and ε4/ε4; n = 180 [53.2%]) vs having the ε3/ε3 genotype (n = 158 [46.7%]).

There were no statistically significant differences in the age at onset of cognitive decline (P = .22) or the age at death (P = .90) between persons with severe CAA and no CAA; however, persons with severe CAA had a longer period between onset of cognitive decline and death than those with no CAA (mean [SD], 10.3 [4.1] vs 9.2 [3.7] years, respectively; P = .006) (Table 2). Persons with severe CAA had slightly fewer years of education than those with no CAA (mean [SD], 14.7 [3.5] vs 15.4 [3.0] years, respectively; P = .02) and were more likely to be of Hispanic ethnicity (6.8% vs 1.3%, respectively; P = .003). There were no statistically significant differences in the prevalence of severe CAA with regard to race (P = .40).

To account for potential differences at the individual ADCs with regard to the prevalence of severe CAA among Hispanic participants, we also performed an ad hoc logistic regression with generalized estimating equations, giving us a population-level effect of Hispanic ethnicity and CAA pathology. Robust standard errors and an independent correlation structure were specified. The model produced results very similar to those of the simple χ² analysis; the odds of having severe CAA were
more than 5 times greater for Hispanic participants compared with non-Hispanic participants \( (P = .007) \).

Among all participants, the presence of severe CAA at autopsy as compared with no CAA was positively predicted by having a history of TIA (12.5% vs 6.1%, respectively; \( OR = 2.1; 95\% CI, 1.0-4.4 \)) and being diagnosed as having probable AD (75.1% vs 65.1%, respectively; \( OR = 1.6; 95\% CI, 1.0-2.4 \)) (Table 3).

When participants were divided into those carrying and not carrying an APOE e4 allele and clinical variables were re-examined, none were significantly associated with the presence of CAA in e4 carriers. In persons with the e3/e3 genotype, however, having a history of stroke was more often observed with severe CAA (6 of 54 participants [11.1%]) than with absence of CAA (4 of 104 participants [3.9%]) \( (OR = 3.8; 95\% CI, 1.0-14.6) \) at autopsy. Also, having hypercholesterolemia was more often observed with severe CAA (27 of 54 participants [50.0%]) than with not having CAA (34 of 104 participants [32.7%]) \( (OR = 2.3; 95\% CI, 1.1-4.7) \).

Participants with severe CAA compared with those without CAA had significantly lower diffuse plaque scores (mean [SD] CERAD score, 1.2 [0.5] vs 1.4 [0.8], respectively; \( P = .01 \)) (Table 2). This effect was more evident in carriers of the APOE e4 allele (\( n = 180 \); mean [SD] CERAD score, 1.1 [0.4] vs 1.4 [0.9], respectively; \( P = .01 \)) than in noncarriers (\( n = 158 \); mean [SD] CERAD score, 1.2 [0.6] vs 1.4 [0.8], respectively; \( P = .20 \)). Participants with severe CAA compared with those without CAA were significantly more likely to have cortical microinfarcts (20.7% vs 12.9%, respectively; \( P = .03 \)), subcortical leukoencephalopathy (20.5% vs 12.1%, respectively; \( P = .02 \)), and cerebrovascular disease (9.3% vs 5.5%, respectively; \( P = .01 \)) (Table 2) identified at autopsy. These effects were not statistically significant within the subgroups defined by carrying and not carrying the APOE e4 allele.

### Table 2. Demographic and Pathological Variables of Persons With Severe CAA and Without Significant CAA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Severe CAA (n = 193)</th>
<th>No CAA (n = 232)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at death, mean (SD), y</td>
<td>79.1 (10.5)</td>
<td>79.3 (11.3)</td>
<td>.90*</td>
</tr>
<tr>
<td>Male, %</td>
<td>59.6</td>
<td>53.5</td>
<td>.20*</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>14.7 (3.5)</td>
<td>15.4 (3.0)</td>
<td>.02*</td>
</tr>
<tr>
<td>Hispanic ethnicity, %</td>
<td>6.8</td>
<td>1.3</td>
<td>.003b</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>94.8</td>
<td>97.0</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>3.6</td>
<td>2.6</td>
<td>.40b</td>
</tr>
<tr>
<td>Other</td>
<td>1.6</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Age at onset of cognitive decline, mean (SD), y</td>
<td>68.6 (10.8)</td>
<td>69.9 (11.4)</td>
<td>.22*</td>
</tr>
<tr>
<td>Time between onset of cognitive decline and death, mean (SD), y</td>
<td>10.3 (4.1)</td>
<td>9.2 (3.7)</td>
<td>.006a</td>
</tr>
<tr>
<td>( \geq 1 ) APOE e4 allele, No./APOE genotype available, No. (%)</td>
<td>107/165 (64.9)</td>
<td>83/194 (42.8)</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>CERAD diffuse plaque score, mean (SD)</td>
<td>1.2 (0.5)</td>
<td>1.4 (0.8)</td>
<td>.01*</td>
</tr>
<tr>
<td>Any cortical microinfarcts, %</td>
<td>20.7</td>
<td>12.9</td>
<td>.03a</td>
</tr>
<tr>
<td>SLEUK, %</td>
<td>20.5</td>
<td>12.1</td>
<td>.02a</td>
</tr>
<tr>
<td>Any hemorrhages, %</td>
<td>9.3</td>
<td>3.5</td>
<td>.01a</td>
</tr>
</tbody>
</table>

### Table 3. Odds Ratios of Clinical Variables in Predicting the Presence of Severe CAA Relative to No CAA in the Entire Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>% Severe CAA (n = 193)</th>
<th>% No CAA (n = 232)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of TIA</td>
<td>12.5</td>
<td>6.1</td>
<td>2.1 (1.0-4.4)</td>
</tr>
<tr>
<td>Diagnosed as having probable AD</td>
<td>75.1</td>
<td>65.1</td>
<td>1.6 (1.0-2.4)</td>
</tr>
</tbody>
</table>

### Discussion

Our study of UDS participants with pathologically confirmed AD found a consistent association of severe CAA at autopsy with neuropathological evidence of brain neurovascular injury including cortical microinfarcts, brain hemorrhages, and subcortical leukoencephalopathy. Clinical expression of cerebrovascular disease was less strong in this population with AD; however, clinically defined TIA-like events were more frequent in patients with severe CAA, and a history of stroke was more common in APOE e3/e3 carriers with severe CAA. In addition, we identified novel potential demographic associations of severe CAA with lower levels of education and Hispanic ethnicity.

Although the UDS is not a population-based study and is therefore subject to enrollment biases, our data provide preliminary support for a higher rate of CAA in Hispanic persons. The post hoc generalized estimating equation analysis, which partly controlled for center-level effects, strengthens this finding. Hispanic ethnicity is a sociocultural construct representing persons of disparate genetic origins, so the biological implications of this observation are unclear. It has been repeatedly shown that Hispanic persons with dementia in the United States are more likely to present for assessment at a more advanced stage of disease and to have diabetes mellitus and arteriosclerotic risk factors associated with vascular dementia, but it is difficult to predict how this would influence our findings of increased CAA prevalence in this population with autopsy-proven AD. It appears that the APOE e4 genotype plays a smaller role in dementia prevalence in Hispanic persons, implicating other genetic and nongenetic factors in the etiology of AD and possibly CAA in these populations. Ethnic differences in CAA prevalence are not well characterized, but a prior study found a higher rate of intracranial hemorrhages, both deep and lobar, in African American persons than in white persons and of deep but not lobar hemorrhages in Hispanic persons. Another study found an increased risk of warfarin-related ICHs in African American, Asian, and Hispanic persons compared with white persons. Although this latter observation could have many possible explanations, it suggests that further research into ethnic differ-
ences in the nature and prevalence of CAA and its consequences is merited.

In our study, having had a TIA or TIA-like episode predicted the presence of severe CAA at autopsy. It is unclear whether these events represent ischemia or manifestations of microhemorrhages, possibly including seizures, but transient focal symptoms are well described in the context of CAA. In a multicenter retrospective cohort study of 172 persons meeting clinical criteria for CAA, 14.5% had a history of transient focal neurological symptoms that consisted of focal paresthesias or weakness, visual disturbances, limb jerking, or dysphasia. Although obtained in a different manner, this number is similar to the 12.5% of our participants with AD and severe CAA on pathology who had a history of TIA-like events at the time they were found to have cognitive decline. Despite the relatively low OR for a history of a TIA-like event predicting the presence of CAA (OR = 2.1), the occurrence of such episodes in elderly persons or those in whom no obvious cardiac or large-artery source of ischemia can be identified should alert physicians to the potential presence of CAA.

When the total group was divided according to carriers and noncarriers of the APOE ε4 allele, distinct clinical patterns emerged. Among noncarriers of the APOE ε4 allele, clinical features of cerebrovascular disease were associated with a higher risk of severe CAA, an effect not evident among carriers of the APOE ε4 allele. Specifically, a known history of stroke and a known history of hypercholesterolemia were significantly more common in persons with severe CAA who had the ε3/ε3 genotype. Pathological studies have provided evidence for the existence of subtypes of CAA, with the APOE ε4 genotype being more strongly associated with the deposition of amyloid in capillaries relative to penetrating arteries and arterioles and to leptomeningeal vessels or in pericapillary areas. Greater CAA in these latter areas in noncarriers of the APOE ε4 allele could predispose to more extensive cerebrovascular ischemia.

We found lower CERAD diffuse plaque scores in patients who had AD with severe CAA relative to those without CAA. As increased severity of CAA is generally correlated with increased parenchymal amyloid plaque pathology, this dissociation is of interest. The relationship between severe CAA and lower parenchymal amyloid pathology was strongest for diffuse plaques in carriers of the APOE ε4 allele and nonsignificant in noncarriers. Apolipoprotein E is involved in the transport of cholesterol and Aβ as well as other soluble molecules, and its isoforms have differential effects on Aβ transport. The APOE ε4 allele prevents the drainage of Aβ via perivascular pathways, possibly explaining a preferential deposition of Aβ in capillaries rather than in the parenchyma in APOE ε4 carriers.

Our study confirms, in a large series of pathologically characterized individuals, the finding that ICH, cortical microinfarcts, and subcortical leukoencephalopathy are more common in persons with severe CAA relative to persons without CAA. This supports the hypothesis that cerebral hemorrhage and ischemia can occur secondary to CAA. However, in light of the manner in which the vascular pathology is documented in the UDS (dichotomized as present or absent, without information regarding its severity or anatomical location), we are unable to further delineate the nature of this relationship. Furthermore, we cannot specifically address the relationship of clinical or genetic variables to the neuroanatomical distribution of CAA in this study.

Our study has several additional limitations. Although the presence of CAA was rated using a common scale at all study sites, the application of this scale was likely heterogeneous across sites. Systematic scales have been created to quantify the topographical extent and severity of CAA, but there is no universally accepted method used across ADCs. However, the dichotomization of cases into the absence of CAA or the presence of severe CAA should serve to mitigate any such intersite differences.

The UDS sample, although relatively large, is one of convenience and is not a population-based sample. It represents participants enrolled in longitudinal observational studies at many centers studying AD across the United States, each of which has its own population and scientific interests. However, each participant underwent a uniform evaluation and diagnosis for which there is standardization, and the heterogeneity of participants may increase the generalizability of the findings.

Conclusions

Being Hispanic and having a history of TIA-like events were significant clinical predictors for the presence of severe CAA in persons found to have AD on neuropathological examination years later. These associations may help clinicians identify persons with cognitive impairment at risk for harboring severe CAA for whom anticoagulation may be contraindicated. Interestingly, we found a lower degree of diffuse amyloid plaque pathology in persons with severe CAA, suggesting differences in Aβ trafficking associated with CAA. Furthermore, a history of stroke and hypercholesterolemia was more common in persons with CAA who do not carry an APOE ε4 allele. The distinct characteristics of APOE ε4-related and non-APOE ε4–related CAA support pathological and genetic studies that suggest divergent pathophysiological mechanisms.
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