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Clinical predictors of severe cerebral amyloid angiopathy and influence of *APOE* genotype in persons with pathologically-verified Alzheimer's disease

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Abstract

Importance—Though cerebral amyloid angiopathy (CAA) has important clinical implications, our understanding of it and ability to diagnose it is limited.

Objective—We sought to determine pathological correlates and clinical factors identifiable during life that predict the presence of severe CAA in persons with pathologically-confirmed Alzheimer's disease (AD).

Design—We compared demographic and clinical variables at the earliest visit during life at which subjects were found to have cognitive impairment, and pathological variables between persons ultimately found to have no or severe CAA at autopsy using logistic regression. Analyses were repeated separately for carriers and non-carriers of the *APOE* ε4 allele.

Setting—Data were obtained from the Uniform Data Set that comprises longitudinal clinical assessments performed in the Alzheimer's Disease Centers funded by the National Institute on Aging.

Participants—193 persons with severe CAA and 232 persons with no CAA. All subjects had cognitive impairment and met NIA-Reagan neuropathological criteria for AD.

Main Outcome Measures—Prevalence of demographic characteristics and the *APOE* ε4 allele and odds ratios of clinical variables for the prediction of severe CAA.

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Dr. Ringman: Administrative support, obtaining funding, study concept and design, acquisition of data, data interpretation, drafting of the manuscript, critical revision of the manuscript for important intellectual content.
Dr. Sachs: Statistical analysis and interpretation.
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Results—Persons with severe CAA were more likely to carry an *APOE* ε4 allele (64.9% vs. 42.8%), to be Hispanic (6.8% vs. 1.3%, p = 0.003), to have had a transient ischemic attack (TIA, 12.5% vs. 6.1%, OR = 2.1, 95% CI = 1 – 4.4), and had lower degrees of diffuse amyloid plaque pathology (mean CERAD scores 1.2 vs. 1.4, p = 0.01) than persons with no CAA. Intracerebral hemorrhage (9.3% vs. 3.5%, p = 0.01), cortical microinfarcts (20.7% vs. 12.9%, p = 0.03), and subcortical leukoencephalopathy (20.5% vs. 12.1%, p = 0.02) were more common in persons with CAA. A higher prevalence of stroke (11.1% vs. 3.9%, OR = 3.8, 95% CI 1.0 – 14.6) and hypercholesterolemia (50% vs. 33.3%, OR = 2.3, CI 1.1 – 4.7) were found in non-carriers of the ε4 allele with severe CAA.

Conclusions and Relevance—Being Hispanic and having had a TIA-like episode were predictors of CAA in persons with AD. Less diffuse parenchymal amyloid pathology in persons with severe CAA suggests a difference in Aβ trafficking.

Introduction

The prevalence of cerebral amyloid angiopathy (CAA) increases with age, being found in the brain of 36% of individuals over 60 years of age and 46% of those over 70[1]. It is more common in persons dying with dementia, being present in 55 to 59%[2] and 80% of those with concurrent Alzheimer's pathology[3]. In addition to possibly contributing independently to cognitive dysfunction[4,5], CAA is associated with an increased risk of spontaneous[6] and anticoagulant-related[7] intracerebral hemorrhage (ICH). It is also associated with a higher risk for vascular complications of anti-amyloid therapies being employed to treat AD[8]. 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 post-mortem examination. Probable and possible CAA require that a lobar ICH has already occurred[9]. Though microhemorrhages are the most common manifestation of CAA on MRI, lobar ICHs can be large and have devastating neurological consequences. The risk of such hemorrhages is increased by anti-platelet and anti-coagulant medications. The microhemorrhages associated with CAA may be asymptomatic but CAA can also present with transient ischemic attack (TIA) – like events[10,11]. Though gradient recalled echo and susceptibility-weighted MRI can sensitively detect microhemorrhages and superficial siderosis of CAA, such MRI techniques still identify the presence of CAA only after ICH. Amyloid imaging using ligands such as 11C-6-OH-BTA-1 (also known as 11C-PIB or PIB) show some promise in identifying CAA during life[12,13] though 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[14,15]. Though the reasons underlying inter-individual differences are largely unknown, they may at least in part be related to genetic variation[15–17]. Variation in the CR1 gene has been found to be related to CAA[18] and it is evident that polymorphisms in the gene encoding for Apolipoprotein E (*APOE*) also play a role[19,20]. The ε4 allele of the *APOE* gene is associated with an increased risk for AD as well as for parenchymal and vascular deposition of derivatives of the amyloid precursor protein, especially Aβ. Persons with the *APOE* ε4 allele

are more likely to develop CAA in capillaries[17] and persons with the ε2 variant are more likely to suffer ICH[21,22]. CAA associated with different *APOE* genotypes may therefore have distinct pathological manifestations and clinical implications.

The aims of the current study were 1) to identify clinical factors associated with the presence of severe CAA in persons with Alzheimer's disease (AD) pathology at the time of autopsy, 2) to assess these associations separately among carriers and non-carriers of the *APOE* ε4 allele, and 3) to assess if there are differences in pathological co-morbidities occurring in persons with severe CAA relative to those without CAA, collectively and separately for carriers and non-carriers of the *APOE* ε4 allele. We analyzed demographic and clinical data from the Uniform Data Set (UDS) of the NIA-funded Alzheimer's Disease Center system in which participants undergo longitudinal comprehensive standardized clinical assessments. A subset of UDS subjects ultimately underwent neuropathological examination and data collected using the Neuropathology Data Set Form[23].

Methods

The National Alzheimer Coordinating Center (NACC) collects the UDS from the network of NIA-funded Alzheimer's Disease Centers (ADC's) in the U.S. Subjects and study partners enrolled in the UDS give informed consent and undergo comprehensive clinical and cognitive evaluations annually at one of the ADCs[23]. At each visit a summary of findings is elaborated and a diagnosis is rendered. A subset of subjects 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.

The brains of subjects undergoing autopsy in the UDS are rated for the degree of CAA present (none, mild, moderate, severe, not assessed, or missing) and undergo semi-quantitative assessments of the density of neurofibrillary tangles (Braak score), neuritic and diffuse plaques (CERAD criteria; sparse, moderate, or frequent plaques), and cerebrovascular pathology. Cerebrovascular pathology is documented as the following being either present or absent: 1) one or more large artery cerebral infarcts (LINF), 2) one or more cortical microinfarcts (MICRO), 3) one or more lacunes (LAC), 4) single or multiple hemorrhages (HEM), and 5) subcortical arteriosclerotic leukoencephalopathy (SLEUK).

Using this database, we identified subjects with cognitive impairment during life who met NIA Reagan criteria for AD at the time of autopsy. For subjects 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 chi-square 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 subject had abnormal cognition for predicting the presence of severe CAA at autopsy (see Table 1 for a comprehensive list of variables studied). Multivariable models were adjusted for age at death, sex, and Hispanic ethnicity. For the subset of subjects for whom *APOE* genotyping was available, these analyses were then repeated separately for carriers and non-carriers of the APOE ε4 allele.

Measures of severity of AD pathological changes (Braak score, CERAD score for diffuse and neuritic plaques) were compared between persons with no CAA and those with severe CAA using t-tests. In addition, the presence or absence of vascular pathology (LINF, MICRO, LAC, HEM, AND SLEUK) was compared between persons with no CAA and severe CAA using chi-square analyses. These analyses were repeated separately for persons known to carry or not carry the *APOE* ε4 allele.

Results

Two hundred thirty-two subjects with NIA-Reagan criteria defined AD and no CAA were compared to 193 subjects with AD and severe CAA. *APOE* genotype was available for 194 (84%) persons with no CAA and 165 (85%) persons with severe CAA. The frequency of severe CAA varied significantly with *APOE* genotype ($p < 0.0001$, Table 2). Persons with the *APOE* ε4/ε4 genotype were more likely to have severe CAA (73.4%) than no CAA (26.6%). Forty-six percent of persons with the ε4/ε3 genotype had severe CAA relative to 34.2% of those with the ε3/ε3 genotype. The presence of at least one copy of the ε4 allele was associated with a higher prevalence of severe CAA relative to no CAA (64.9% vs. 42.8%). In this population of persons with pathologically-confirmed AD, the frequency of persons with any *APOE* ε2 allele was low (n = 21 or 6%). Therefore, for analyses of effects of the ε4 allele, subjects with any ε2 allele were excluded and the remaining subjects dichotomized into those having one or two ε4 alleles (i.e. ε4/ε3 and ε4/ε4, n = 180 or 53.2%) vs. being of the ε3/ε3 genotype (n = 158 or 46.7%).

There were no statistically significant differences in the age of onset of cognitive decline or the age of death between persons with severe CAA and no CAA; however, subjects with severe CAA had a longer period between onset of cognitive decline and death (10.3 vs. 9.2 years, $p = 0.006$, Table 3). Subjects with severe CAA had slightly fewer years of education than those with no CAA (14.7 vs. 15.4, $p = 0.02$) and were more likely to be of Hispanic ethnicity (6.8% vs. 1.3%, $p = 0.003$). There were no statistically significant differences in the prevalence of severe CAA with regard to race.

In order to account for potential differences at the individual ADCs with regard to the prevalence of severe CAA among Hispanics, we also performed an ad-hoc logistic regression with Generalized Estimating Equations (GEE), 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 very similar results to those of the simple chi-square analysis; the odds of having severe CAA were over five times greater for Hispanics compared to non-Hispanics ($p = 0.007$).

Among all subjects, having a history of TIA (12.5% vs. 6.1%, OR = 2.1, 95% CI 1.1 - 4.4) and being diagnosed with probable AD (75.1% vs. 65.1%, OR = 1.6, 95% CI 1.0 – 2.4) positively predicted the presence of severe CAA at autopsy (Table 4).

When subjects were divided into those carrying and not-carrying an *APOE* ε4 allele and clinical variables re-examined, none were significantly associated with the presence of CAA in ε4 carriers. In persons of the ε3/ε3 APOE genotype, however, having had a history of stroke was more often observed with severe CAA (6/54 or 11.1%) than with absence of CAA (4/104, 3.9%, OR = 3.8, CI 1.0 – 14.6) at autopsy. Also, having hypercholesterolemia was more often observed with severe CAA (27/54, 50%) than with not having CAA (34/104 or 33.3%, OR = 2.3, CI 1.1 – 4.7).

Subjects with severe CAA had significantly lower diffuse plaque scores (1.2 vs. 1.4, p = 0.01, Table 3). This latter effect was more evident in carriers of the *APOE* ε4 allele (n = 180, 1.1 vs. 1.4, p = 0.01) than in non-carriers (n = 158, 1.2 vs. 1.4, p = 0.2). Subjects with severe CAA were significantly more likely to have cortical microinfarcts (20.7% vs. 12.9%, p = 0.03), subcortical leukoencephalopathy (20.5% vs.12.1%, p = 0.02), and cerebral hemorrhages (9.3% vs. 3.5%, p = 0.01, Table 3) identified at autopsy than those without CAA. These effects were not statistically significant within the subgroups defined by carrying and not carrying the *APOE* ε4 allele.

Discussion

Our study of UDS subjects 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 AD population, although clinically-defined TIA-like events were more frequent in patients with severe CAA and a history of stroke more common in *APOE* ε3/3 carriers with severe CAA. In addition, we identified novel potential demographic associations of severe CAA with lower levels of education and Hispanic ethnicity.

Though 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 Hispanics. The post-hoc GEE analysis which partly controlled for center-level effects strengthens this finding. Hispanic ethnicity is a socio-cultural construct representing persons of disparate genetic origins so the biological implications of this observation are unclear. It has been repeatedly show that Hispanics with dementia in the U.S. are more likely to present for assessment at a more advanced stage of disease[24,25] and have diabetes[26] and arteriosclerotic risk factors associated with vascular dementia[27,28] 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* ε4 genotype plays a smaller role in dementia prevalence in Hispanics[24,25], implicating other genetic[29] and non-genetic 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-Americans than in Caucasians and of deep,

but not lobar hemorrhages in Hispanics[30]. Another study found an increased risk of warfarin-related ICH's in African-Americans, Asians, and Hispanics compared to whites[31]. Though this latter observation could have many possible explanations, it suggests that further research into ethnic differences 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. Whether these events represent ischemia or manifestations of microhemorrhages, possibly including seizures[32], is unclear but transient focal symptoms are well described in the context of CAA[10]. In a multicenter retrospective cohort study of 172 persons meeting clinical criteria for CAA, 14.5% had a history of transient focal neurological symptoms which consisted of focal paresthesias or weakness, visual disturbances, limb jerking, or dysphasia[11]. Though obtained in a different manner, this number is similar to the 12.5% of our subjects with AD and severe CAA on pathology who had histories of TIA-like events at the time when they were found to have cognitive decline. Despite the relatively low odds ratio for a history of a TIA-like event in predicting the presence of CAA (2.1), the occurrence of such episodes in the elderly or in persons 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 non-carriers of the *APOE* ε4 allele, distinct clinical patterns emerged. Among non-carriers of the *APOE* ε4 allele, clinical features of cerebrovascular disease were associated with a higher risk for severe CAA, an effect not evident among carriers of the *APOE* ε4 allele. Specifically, having a known history of stroke and hypercholesterolemia were significantly more common in persons with severe CAA who were of the ε3/3 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, leptomeningeal vessels, or in pericapillary areas[15,17]. Greater CAA in these latter areas in non-ε4 carriers could predispose to more extensive cerebrovascular ischemia.

We found lower CERAD diffuse plaque scores in AD patients with severe CAA relative to those without CAA. As increased severity of CAA is generally correlated with increased parenchymal amyloid plaque pathology[14], 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 non-significant in non-carriers. Apolipoprotein E is involved in the transport of cholesterol and Aβ as well as other soluble molecules and its isoforms have differential affects on Aβ transport[33,34]. *APOE* ε4 prevents the drainage of Aβ via perivascular pathways[35], possibly explaining a preferential deposition of Aβ in capillaries rather than in the parenchyma in *APOE* ε4 carriers[34,35].

Our study confirms, in a large series of pathologically characterized individuals, the finding that intracerebral hemorrhage, 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 neuroanatomic distribution of CAA in the current study.

This study has several additional limitations. Though the presence of CAA was rated using a common scale at all study sites, the application of this scale was likely to be heterogenous across sites. Systematic scales have been created to quantify the topographical extent and severity of CAA[36,37], but there is no universally accepted method employed across ADCs. The dichotomization of cases into the absence of CAA or the presence of severe CAA should serve to mitigate any such inter-site differences, however.

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

In summary, we found that 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 pathophysiologic mechanisms.

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Table 1

Uniform Data Set variables studied in regression analyses.

Medical History: **1)** Heart attack/cardiac arrest **2)** Stroke **3)** Transient ischemic attack **4)** "Other" cerebrovascular Dx **5)** Seizures **6)** "Other" neurological Dx **7)** Hypertension **8)** Hypercholesterolemia **9)** Diabetes	Hachinski Scale: **13)** Abrupt onset **14)** Stepwise decline **15)** Emot. incontinence **16)** Focal symptoms **17)** Focal signs	Presence of exam findings suggestive of CNS disorder: **20)** Absent **21)** Focal deficits **22)** Gait abnormality **23)** Eye movement abnormalities
Cognitive deficits at presentation by history: **10)** Visuospatial **11)** Attention/concentration **12)** Fluctuations	**18)** What was the first cognitive symptom? **19)** What was the clinical course of the illness? (gradually progressive, stepwise, static, fluctuating, improved)	**24)** What was the clinical diagnosis for the cause of the illness?

Table 2

Distribution of *APOE* genotypes in the study population relative to presence or absence of severe CAA (χ^2 = 31.03, df = 4, $p < 0.0001$).

APOE Genotype	Severe CAA (n = 165)	No CAA (n = 194)
e3,e3	54 (34.2%)	104 (65.8%)
e3,e4	53 (45.7%)	63 (54.3%)
e2,e3	4 (36.4%)	7 (63.6%)
e4,e4	47 (73.4%)	17 (26.6%)
e2,e4	7 (70.0%)	3 (30.0%)

Table 3

Demographic and pathological variables of persons with severe CAA and without significant CAA.

	Severe CAA (n = 193)	**No CAA (n = 232)**	
Age at the time of death (s.d.)	79.1 (10.5)	79.3 (11.3)	*p = 0.90
Male (%)	59.6%	53.5%	**p = 0.20
Education in years (s.d.)	14.7 (3.5)	15.4 (3.0)	*p = 0.02
Hispanic ethnicity (%)	6.8%	1.3%	**p = 0.003
Race %			**p = 0.40
White	94.8	97	
African-American	3.6	2.6	
Other	1.6	0.4	
Age of onset of cognitive decline (s.d.)	68.6 (10.8)	69.9 (11.4)	*p = 0.22
Years from onset of cognitive decline to death (s.d.)	10.3 (4.1)	9.2 (3.7)	*p = 0.006
# (%) with at least one *APOE* ε4 allele	107/165 (64.9%)	83/194 (42.8%)	**p < 0.0001
Mean CERAD diffuse plaque score (s.d.)	1.2 (0.5)	1.4 (0.8)	*p = 0.01
Percent with any cortical microinfarct (MICRO)	20.7%	12.9%	**p = 0.03
Percent with subcortical leukoencephalopathy (SLEUK)	20.5%	12.1%	**p = 0.02
Percent with any hemorrhage (HEM)	9.3%	3.5%	**p = 0.01

* represents results of t-tests,

** represents results of chi-square tests.

Table 4

Odds ratios of clinical variables in predicting the presence of severe CAA (relative to no CAA) in the entire cohort.

	Severe CAA (n = 193)	**No CAA (n = 232)**	
History of TIA (%)	12.5%	6.1%	OR = 2.1 (1.0–4.4)
Diagnosed with probable AD (%)	75.1%	65.1%	OR = 1.6 (1.0 – 2.4)