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Cerebral amyloid angiopathy and its co-occurrence with Alzheimer's disease and other cerebrovascular neuropathologic changes

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Abstract

We examined the relationship between cerebral amyloid angiopathy (CAA), Alzheimer's disease neuropathologic changes (ADNC), other vascular brain pathologies, and cognition in a large multi-center autopsy sample. Data was obtained from the National Alzheimer's Coordinating Center on autopsied subjects (N=3,976) who died between 2005 and 2012. Descriptive statistics and multivariable regression models estimated the associations between CAA and other pathologies, and between CAA severity and cognitive test scores proximal to death. CAA tended to co-occur with ADNC but a substantial minority of cases were discrepant. CAA was absent in 22% (n= 520) of subjects with frequent neuritic plaques but present in 20.9% (n=91) of subjects with no neuritic plaques. In subjects with no/sparse neuritic plaques, non-hemorrhagic brain infarcts were more common in those with CAA pathology than without ($P= 0.007$). In subjects without the APOE $\epsilon 4$ allele, CAA severity was associated with lower cognition proximal to death, factoring in other pathologies. The presence of CAA in non-AD patients may indicate a distinct cerebrovascular condition.

Keywords

Cerebral amyloid angiopathy; Alzheimer's disease neuropathologic change; cerebrovascular disease; neuropathology; cognition

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1. INTRODUCTION

Cerebral amyloid angiopathy (CAA) is a common neuropathological finding among older adults, especially among those who meet neuropathologic criteria for Alzheimer's disease (AD) (Smith and Greenberg, 2009; Vinters, 1987). CAA is characterized by A β deposits in blood vessel walls (Vinters, 1987). CAA is considered an important cause of lobar intracerebral hemorrhages and some evidence suggests that CAA has a broader impact on cerebrovascular function (Attems et al., 2008; Smith et al., 2008; Soontornniyomkij et al., 2010). Additionally, CAA is linked to the maladaptive inflammatory response to anti-A β immunotherapy in AD clinical trials (Eng et al., 2004; Nicoll et al., 2003). As this brain condition combines Alzheimer's-type (A β) and cerebrovascular changes, it is important to understand the relationship between CAA and other brain pathologies.

Many studies have documented associations between CAA and AD neuropathologic change (ADNC), defined by the National Institute on Aging and Alzheimer's Association (NIA-AA) criteria as comprising A β plaques, neuritic amyloid plaques, and neurofibrillary tangles (Hyman et al., 2012; Montine et al., 2012); however CAA may occur in the absence of ADNC (Attems et al., 2005; Ellis et al., 1996; Fernando and Ince, 2004; Kövari et al., 2012; Pfeifer et al., 2002; Thal et al., 2003; Xuereb et al., 2000; Yamada, 2002). An estimated 78–98% of individuals with ADNC also have CAA (Jellinger, 2002), but only about 25% of patients with ADNC also have severe CAA (Ellis et al., 1996). CAA has also been linked to other vascular pathologies, in particular cerebral hemorrhages and infarcts (Smith and Greenberg, 2009). Amyloid deposition likely weakens the cerebral vessel walls facilitating rupture leading to hemorrhages (Vinters, 1987). CAA may also lead to ischemia; studies have found increased prevalence of cerebral infarcts and microinfarcts as well as subcortical white matter lesions in cases of severe CAA (Holland et al., 2008; Kimberly et al., 2009; Ringman et al., 2014; Soontornniyomkij et al., 2010).

The presence of CAA in patients with AD may have a greater clinical impact than AD alone (Jellinger, 2002; Thal et al., 2003). Severe CAA has also been associated with cognitive decline independent of AD (Arvanitakis et al., 2011; Keage et al., 2009). However, the association between CAA and cognition may disappear after adjustment for ADNC (Thal et al., 2003; Nelson et al., 2010). More data are required from large datasets to better characterize the relationship between CAA, ADNC, other vascular brain pathologies, and cognition.

APOE ϵ 4 allele status, a strong risk factor for AD (Corder et al., 1993), is also associated with increased frequency of CAA (Attems et al., 2008, 2005; Nelson et al., 2013; Pfeifer et al., 2002; Ringman et al., 2014; Tanskanen et al., 2005; Thal et al., 2003). Patients with at least one APOE ϵ 4 allele are more likely to have severe CAA (Attems et al., 2005; Thal et al., 2003) as well as a subtype of CAA with amyloid deposits in capillaries in addition to larger blood vessels (Grinberg and Thal, 2010; Thal et al., 2002). History of stroke and hypercholesterolemia has been associated with severe CAA in AD but only among those without any APOE ϵ 4 alleles (Ringman et al., 2014). In another study, CAA and small vessel disease were positively correlated but only among in those with APOE ϵ 4 allele (Esiri

et al., 2015). Since there are ongoing clinical approaches that use APOE ϵ 4 carrier status in selection criteria, it would be desirable to understand according to APOE genotype.

This study focused on CAA pathology and used data from a large multi-center database maintained by the National Alzheimer's Coordinating Center (NACC). The NACC database comprises individuals who were evaluated by one of the Alzheimer's Disease Centers (ADCs) funded by National Institute on Aging. The primary objectives of this study were to describe 1.) co-occurrence of CAA with ADNC, particularly neuritic plaques, in autopsied older adults; 2) clinical and pathologic features of participants with and without co-occurring CAA and neuritic plaques; and 3) the association between CAA severity and cognition adjusting for ADNC and other pathologies. This research may help identify subtypes of CAA in patients with and without AD.

2. METHODS

2.1. Data Source and Study Sample

Data for this analysis was obtained from NACC's Minimum Data Set (MDS), Uniform Data Set (UDS), and Neuropathology Data Set (Beekly et al., 2004; Morris et al., 2006; Beekly et al., 2007). NACC data sets consist of information on subjects who were previously evaluated at one of 34 past and present ADCs located throughout the U.S. Each ADC operates independently—recruiting and enrolling subjects according to their own protocols. Subjects generally responded to recruiting efforts to participate in a research study or because they were referred to the ADC due to concerns about their health, cognition, or behavior. Subjects can enroll with any level of cognition, ranging from normal to demented. The MDS includes single record diagnostic data collected retrospectively for participants evaluated from 1984 through 2005 and the UDS includes standardized clinical, neuropsychological, and diagnostic data from participants who were evaluated longitudinally after September, 2005. Data were collected by trained clinicians and interviewers and methods and rationale for the MDS and UDS have been previously published (Beekly et al., 2004; Morris et al., 2006; Beekly et al., 2007). Informed consent was obtained from all participants at the individual ADCs. ADCs had IRB approval and research using NACC data was approved by the University of Washington Human Subjects Division.

Subjects (n=5,734) were eligible for this study if they had died and been autopsied at an ADC between January 2002 and December 2012 and were aged 65 years or older at death. Subjects (n= 1,064) with rare neurological diseases based on autopsy findings were excluded (including those with frontotemporal lobar degeneration, prion disease, brain cancer, and genetic abnormalities). Subjects (n=694) were excluded from this study if they were missing data on CAA severity, CERAD stage of neuritic plaque densities (Mirra et al., 1991), or Braak stage for neurofibrillary tangles (Braak et al., 2006). The final sample included 3,976 autopsied subjects.

2.2. Measures

2.2.1. Pathologic Features at Autopsy—Neuropathological evaluations were conducted by individual ADCs according to their own protocols. These protocols may differ

between ADCs but conform to consensus guidelines. Results were entered into the NACC database using a standardized NACC form. Presence of CAA was detected using amyloid stains (e.g. Congo red, thioflavin-S, or A β immunostaining) as determined by each ADC's protocol. CAA was graded semi-quantitatively as none, mild, moderate, or severe. As per NACC coding guidelines, severity was based on the neuropathologist's "estimate of overall severity rather than an individual vessel". For analytic purposes, CAA was also categorized as present (any severity CAA) vs. absent (no CAA) to reduce potential heterogeneity in severity scoring.

A β plaque frequency was assessed by Consortium to Establish a Registry for Alzheimer's Disease (CERAD) stages of diffuse and neuritic plaque densities (frequent, moderate, sparse, or none) (Mirra et al., 1991). Neurofibrillary degeneration was assessed by categorical Braak staging (Stages 0, I/II, III/IV, V, VI) (Braak et al., 2006). For the purpose of plotting trend by age, ADNC was also categorized in this study by severity as: *High* ADNC (Braak stages V/VI + frequent neuritic plaques); *Low to Intermediate* ADNC (Braak stages 0-IV + frequent neuritic plaques, OR Braak stage 0-VI + moderate or sparse neuritic plaques, OR Braak stages I-VI + no neuritic plaques); or *No* ADNC (No neuritic plaques, no neurofibrillary tangles). The new NIA-AA criteria additionally includes Thal phases for A β plaques (Thal et al., 2002), however, this staging was not available for the subjects in this retrospective analysis. Thus, our operationalization of ADNC overlaps but does not correspond exactly to ADNC levels as defined by new NIA-AA criteria (Hyman et al., 2012; Montine et al., 2012). In contrasting severity of CAA and ADNC, this study focused on the co-occurrence of vascular A β deposits (CAA) with neuritic plaques since they may share pathogenic processes (Biffi and Greenberg, 2011; Viswanathan and Greenberg, 2011). Subjects with no/sparse neuritic plaques were considered to have minimal amyloid plaques. Diffuse plaques, which are defined as "plaques with non-compact amyloid and no apparent dystrophic neurites" were additionally considered in sensitivity analyses to account for other types of amyloid plaques.

In addition, presence of other pathologies were documented. Hemorrhages, gross infarcts (larger artery and lacunar), microinfarcts, and subcortical arteriosclerotic leukoencephalopathy were noted as present or absent if assessed. Hemorrhages included any cerebral hemorrhages, regardless of size. Large artery infarcts was defined according to NACC coding guide as an infarct of any histologic age "larger than 1 cm in diameter in the distribution of large and medium meningocerebral vessels." Lacunes were defined as one or more "cystic/old infarcts or hemorrhages 1-cm or less in diameter that are usually grossly identified and in the distribution of small parenchymal vessels." Microinfarcts were defined as infarcts detected microscopically and not grossly visible regardless of histologic age. The presence of any cortical microinfarcts (yes or no) was recorded. Arteriolosclerosis was recorded as none, mild, moderate, or severe. Medial temporal lobar sclerosis, including hippocampal sclerosis was also noted as present or absent if assessed. Lewy bodies were categorized as none, brainstem predominant, limbic (transitional), and neocortical (diffuse) (McKeith et al., 2005).

2.2.2. Clinical Characteristics—Demographic information assessed in both the MDS and UDS included: sex, race/ethnicity, highest level of education achieved. Health history

was collected in the UDS via structure interviews; vascular risk factors included history of or currently active hypertension, hypercholesterolemia, or diabetes, as well as smoking history (yes/no, ever smoked 100 cigarettes or more. Using all available information, clinicians recorded cognitive status (normal, impaired not MCI, MCI, or dementia) at each visit and determined a clinical diagnosis indicating the suspected etiology of cognitive impairment for those with impaired cognition. Overall cognition was measured in both data sets using the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). Overall cognitive and functional impairment as quantified by the Clinical Dementia Rating “sum of boxes” score (CDR-SB) (Morris, 1993) was measured in the UDS only. APOE genotype is available for only a subset of participants (n= 2,985 of 3,976). For this study, APOE ϵ 4 allele status was categorized as none or at least one APOE ϵ 4 allele.

2.3. Statistical analyses

The proportion of subjects with CAA was estimated overall across ADCs, and within each ADC. Participant demographics and clinical dementia status at last visit were described according to severity of CAA. Age-related trends in the proportion of subjects with CAA and ADNC were described using fitted polynomial curves. Next we examined the correlation between neuritic plaque densities and the severity of CAA.

Among subjects with and without co-occurring CAA and neuritic plaques, participant demographics and pathological features were first described to find correlates of co-occurrence or independence. Pearson χ^2 test or Fisher’s exact test (if any categories included <10 subjects) were used to compare categorical measures and ANOVA was used to compare continuous measures. In a sub-sample of UDS-only subjects the presence of vascular risk factors (hypertension, hypercholesterolemia, or diabetes, as well as smoking history) as of the last clinical visit was also examined according to CAA and neuritic plaque co-occurrence among subjects without an APOE ϵ 4 allele.

Two multivariable linear regression models estimated the association of CAA severity with (1) MMSE and (2) CDR-SB scores proximal to death. Generalized estimating equations with an exchangeable correlation matrix accounted for potential correlation of MMSE or CDR-SB scores within ADCs. To estimate the contribution of CAA to cognition above and beyond the contribution of other pathologies, models included adjustment for AD pathology (neuritic plaques and Braak staging), neocortical Lewy bodies, vascular lesions (hemorrhages, gross infarcts, and microinfarcts), and medial temporal lobar sclerosis, as well as demographics (age at death, education, non-white race, and years between death and last visit). The analysis between CAA and MMSE only included participants with a MMSE evaluation that was known to have occurred within 2 years prior death, in order to exclude those with potentially long lag times between the clinical visit and death. The analysis between CAA and CDR-SB scores was limited to UDS participants with a clinical visit within 2 years prior to death. We examined whether the associations between CAA severity and cognitive test scores differed by APOE ϵ 4 allele status by including an interaction between CAA and APOE ϵ 4 allele variables. Statistical analyses were performed using STATA 12.0. All tests were two-tailed with α -levels set to 0.05.

3. RESULTS

This sample of 3,976 autopsied subjects was drawn from 34 ADCs (range: 2 to 396 subjects per ADC; average: 116.9 subjects per ADC). The mean age of death was 83.2 (SD: 8.4) and 50.3% of subjects were female (n=1,999). Subjects were mainly white (n=3,786; 95.2%) and well educated (n=2,655; 66.8% with above high school education). The majority of subjects were demented at their last clinical visit (n=3,157; 79.4%), however subjects ranged from 0 (severe cognitive impairment) to 30 (normal cognition) on the MMSE, with an average score of 16.2 (SD: 9.6). About half of the 2,985 subjects with APOE genotyping obtained had at least one APOE ϵ 4 allele (n=1,558; 52.2%). The percentage of subjects with CAA present at autopsy varied by ADC; CAA was present in 0.0–30.0% with no ADNC, 28.0–69.6% with low to intermediate ADNC, and 51.5–97.6% with high ADNC, among ADCs with at least 30 subjects per ADNC strata. CAA was observed in the majority of subjects; 547 (13.7%) had severe CAA; 854 (21.5%) had moderate CAA and 1,211 (30.5%) had mild CAA. Overall, subjects with more severe CAA were more likely to be demented at last clinical visit and have at least one APOE ϵ 4 allele (Table 1). However, subject demographics were relatively similar regardless of CAA severity (Table 1).

The proportion of subjects with CAA was relatively similar across ages, with a slight decrease after age 80 (Figure 1). The proportion of autopsied subjects with high ADNC decreased after approximately age 70 (Figure 1). A similar trend was observed for the proportion of those with at least one APOE ϵ 4 allele. On the other hand, presence of low to intermediate ADNC increased by age at death beyond age 80.

Subjects with more dense CERAD neuritic plaques were more likely to have moderate or severe CAA (Figure 2). However, a majority of subjects had no or mild CAA, even among those with frequent neuritic plaques. Absence of CAA was common in subjects with a lower density of neuritic plaques. Approximately 20% of cases with no neuritic plaques had some CAA pathology noted and approximately 20% of cases with frequent neuritic plaques had no CAA pathology noted.

Clinical and pathologic characteristics of subjects differed according to whether they had co-occurring CAA and neuritic plaques or not (Table 2). The presence of at least one APOE ϵ 4 allele was more likely among those with CAA, however a substantial proportion of those with no CAA and moderate/frequent neuritic plaques had at least one APOE ϵ 4 allele. Subjects with CAA but no/sparse neuritic plaques were more likely to be older, male, and less educated than those without any CAA or those with co-occurring CAA plus moderate/frequent neuritic plaques. Subjects with CAA but no/sparse neuritic plaques were also more likely to have hemorrhages, gross infarcts, microinfarcts, and moderate/severe arteriolosclerosis.

Collectively, non-hemorrhagic vascular lesions (gross infarcts and microinfarcts) were more common in subjects with any CAA compared to subjects without CAA among subjects with no/sparse neuritic plaques (Figure 3). Since moderate/frequent diffuse plaques were more common in those with CAA (Table 2), this analysis was rerun excluding subjects with moderate/frequent diffuse plaques in addition to moderate/frequent neuritic plaques,

however results remained essentially unchanged (55% of subjects with CAA vs 41% of subjects without CAA had non-hemorrhagic infarcts). Subsequently, we also reran analyses excluding individuals with Braak Stage III or higher; results were similar but the association was weaker (49% of subjects with CAA vs 40% of subjects without CAA had non-hemorrhagic infarcts, $P=0.06$). Among subjects with CAA, the proportion of those with Braak Stage III or higher in those with (49.3%) and without infarcts (45.0%) did not differ significantly ($P=0.49$).

We further examined subjects without APOE $\epsilon 4$ allele, to see if cardiovascular risk factors may be a non-APOE $\epsilon 4$ related factor associated with CAA. However, there were no differences in history of smoking, hypertension, hypercholesterolemia, or diabetes across CAA status among 527 UDS subjects who had health history information collected (Table 3).

Among 2,009 subjects who had MMSE scores within two years of death and no APOE $\epsilon 4$ allele, those with CAA had significantly lower MMSE scores at last visit compared to those with no CAA (Table 4) even after adjustment for other neuropathologies and demographics. Scores were associated in a graded fashion with increasing severity of CAA. However, among those with at least one APOE $\epsilon 4$ allele, CAA was not associated with MMSE scores after adjustment for other neuropathologies and demographics. Findings were similar for CDR-SB among the subset of UDS subjects ($n=963$) who were evaluated clinically after 2005: among subjects with no APOE $\epsilon 4$ allele, CDR-SB scores increased (scores are inverted in Table 4) with increasing severity of CAA. Subjects with at least one APOE $\epsilon 4$ allele, compared to subjects without the APOE $\epsilon 4$ allele, tended to have more severe ADNC (66.6% vs. 36.2% high ADNC) and cognitive impairment (the mean MMSE was 18.7 (SD: 9.5) vs. 13.5 (SD: 9.1) points) (both $P<0.001$).

4. DISCUSSION

We examined clinical and other pathologic correlates of CAA in the large NACC autopsy dataset. CAA was a common finding among autopsied subjects, however, we found substantial variation of the frequency of CAA by ADNC between different research centers. Clinical and pathologic characteristics differed between subjects with and without co-occurring CAA and neuritic plaques. CAA severity was associated with lower cognition at last visit among those without an APOE $\epsilon 4$ allele. In a novel result, among individuals with minimal amyloid plaques, the presence of any severity of CAA was correlated with non-hemorrhagic brain infarcts.

These results add to prior evidence that CAA pathology is frequent among older adults, in particular in those with comorbid ADNC (Attems et al., 2005; Ellis et al., 1996; Fernando and Ince, 2004; Kövari et al., 2012; Pfeifer et al., 2002; Thal et al., 2003; Xuereb et al., 2000; Yamada, 2002). CAA severity was relatively stable over different ages, but similar to ADNC in terms of general trends. The proportion of any CAA and high ADNC was decreased after age at death of 80 years, perhaps a reflection of the age-related trends in the APOE $\epsilon 4$ allele. In comparison, some previous studies have reported increased prevalence of

CAA with age (Attems et al., 2008; Kövari et al., 2012; Thal et al., 2008; Vinters and Gilbert, 1983).

Interestingly, among subjects with no/sparse neuritic plaques, comorbid vascular conditions, including gross infarcts and microinfarcts, were more likely in subjects with CAA compared to subjects without CAA. This relationship remained even after excluding subjects with moderate/frequent diffuse plaques or Braak Stages III or higher. Although, CAA is classically linked to lobar intracerebral hemorrhages, ischemic infarcts (gross or microscopic) have previously only been associated with severe CAA in individuals with AD (Olichney et al., 2000, 1997; Ringman et al., 2014), dementia (Soontornniyomkij et al., 2010), or in those with clinically diagnosed CAA (Kimberly et al., 2009). This study extends these findings to individuals with no/low ADNC and with any severity of CAA at autopsy. Neurofibrillary tangle severity may also differ by CAA phenotypes (Charidimou et al., 2015), however we did not find significant differences in presence of tangles in CAA subjects with minimal neuritic plaques.

The etiology of non-hemorrhagic brain infarcts linked to CAA is unclear. CAA may impair regulation of cerebral blood flow, which could lead to subsequent vascular brain injury (Smith and Greenberg, 2009). An alternative hypothesis is that CAA could be enhanced by small vessel disease (Grinberg and Thal, 2010). CAA could represent an effect of vascular dysfunction, particularly in cases of CAA in APOE $\epsilon 4$ negative individuals without ADNC. However, in this study vascular risk factors were not associated with CAA in APOE $\epsilon 4$ negative subjects.

Our results add to extensive evidence of an association between APOE $\epsilon 4$ and CAA (Attems et al., 2008, 2005; Nelson et al., 2013; Pfeifer et al., 2002; Ringman et al., 2014; Tanskanen et al., 2005; Thal et al., 2003), which suggest that vascular amyloid may be preferentially deposited in those with the APOE $\epsilon 4$ allele independent of ADNC. Interestingly, the association between CAA and cognition was only present in those without the APOE $\epsilon 4$ allele. Subjects with the APOE $\epsilon 4$ allele tended to have more severe ADNC and lower cognition; perhaps among individuals with APOE $\epsilon 4$ allele cognition is more strongly influenced by severity of ADNC. Future studies should further examine the role of APOE genotype on CAA subtypes in more diverse samples. For instance, the APOE $\epsilon 2$ allele is also associated with increased CAA and clinical presentation of hemorrhages (Charidimou et al., 2015). Few participants had an APOE $\epsilon 2$ allele, so APOE $\epsilon 2$ was not considered in this study.

This study provides evidence that CAA is associated with lower cognition prior to death in those no APOE $\epsilon 4$ alleles. CAA has been associated with dementia (Tanskanen et al., 2005; Xuereb et al., 2000), decline in episodic memory and processing speed (Arvanitakis et al., 2011) and worsening cognitive impairment (Pfeifer et al., 2002; Serrano-Pozo et al., 2013). However, other studies (some of which included more quantitative metrics of ADNC) found no association after adjustment for AD (Nelson et al., 2010; Thal et al., 2003). In this study, CAA was associated with lower MMSE and CDR-SB scores in a graded fashion. Some negative findings in smaller studies could be potentially explained by their use of dichotomous measures, which could dilute the association between more severe CAA and

cognition. Alternatively, our use of semi-quantitative measures of ADNC may have resulted in incomplete adjustment for AD-related pathologies.

The NACC dataset is one of the largest, high-quality composite datasets with detailed autopsy information. However there are some important limitations related to this retrospective analysis. NACC data is not a population-based cohort, and biases have been detected in autopsy cohorts that derive from memory clinics (Schneider et al., 2009; Tsuang et al., 2005). Some participants were excluded from analyses due to missing data, in particular APOE genotype. CAA deposited in capillaries (capillary CAA) is associated with APOE $\epsilon 4$ alleles (Thal et al., 2010), however, information on distribution of CAA was not available. Additionally, there was no standard method for evaluating CAA presence or staging criteria across ADCs, and different Centers may have used different stains or assessment protocols. This heterogeneity is an important limitation and may have resulted in variation in CAA classification. However, given the variations between centers it could be argued that a multi-centered approach would be more generalizable than a single-center study. Further, the strong correlations found between CAA severity and neuritic plaques densities as well as cognitive status at last visit suggests that the CAA staging among all ADCs combined was meaningful.

Taken along with the caveats should be the appreciable strengths of using the NACC dataset. NACC data is extensively audited and represents a large population of clinical research volunteers. The multicenter derivation of these data provides opportunities as well as potential pitfalls. This sample allowed us to examine the variation in CAA and ADNC estimates between individual medical centers, which have differing study populations, recruitment procedures, and study protocols. The extensive neuropathologic and clinical data allowed for comparisons between subjects with varying levels of CAA, ADNC, and cerebrovascular disease as well as the relationship between CAA severity and cognition proximal to death.

In summary, the strengths of the NACC dataset enabled a study of clinical and pathological features related to CAA, which is a common finding at autopsy. Although CAA and ADNC are associated, they do not always co-occur. Moderate to severe CAA may be independently associated with lower cognition, particularly among those without APOE $\epsilon 4$ alleles. Co-occurrence of CAA and ADNC in those with APOE $\epsilon 4$ allele may represent pathogenic tendencies. Meanwhile co-occurrence of CAA and ADNC in those without an APOE $\epsilon 4$ allele, or in those with CAA but no ADNC may be associated with additional underlying vascular conditions. In conclusion, our study points towards pathologically-definable subtypes of CAA, the clinical relevance of which may be better delineated in the future.

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Abbreviations

AD	Alzheimer's disease
ADNC	Alzheimer's disease neuropathologic changes
CAA	cerebral amyloid angiopathy
CDR-SB	clinical dementia rating sum of boxes
CI	confidence interval
MMSE	mini-mental state examination
NACC	National Alzheimer's Coordinating Center

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Highlights

- We examined characteristics of cerebral amyloid angiopathy (CAA) pathology.
- CAA is common in AD but also was found in the absence of neuritic plaques.
- Cerebrovascular infarcts were linked to CAA in those with minimal amyloid plaques.
- CAA severity was associated with cognition in APOE ϵ 4 negative subjects.

NACC autopsies: CAA (a), ADNC (b), and APOE (c) by age at death

Figure 1.

Presence of cerebral amyloid angiopathy (CAA), Alzheimer's disease neuropathologic change (ADNC), and at least one APOE $\epsilon 4$ allele by age at death. The proportion of subjects with CAA (a), ADNC (b), and at least one APOE $\epsilon 4$ allele (c) was plotted according to age at death using fitted polynomial curves.

Figure 2.
Percentage of autopsies with none, mild, moderate, and severe cerebral amyloid angiopathy (CAA) according to CERAD neuritic plaque densities.

Figure 3. Gross or microscopic infarcts in subjects with cerebral amyloid angiopathy (CAA+) compared to those without (CAA-). This figure focuses on 824 subjects (of 846) with no/sparse neuritic plaques and non-missing vascular pathology details.

Table 1

Participant characteristics by severity of cerebral amyloid angiopathy

	Cerebral Amyloid Angiopathy			
	None (n=1,364)	Mild (n=1,211)	Moderate (n=854)	Severe (n=547)
	N (%) unless otherwise noted			
Clinical Characteristics				
Age at death (years), Mean (SD)	84.0 (8.7)	83.2 (8.6)	82.5 (8.1)	82.4 (7.7)
Female sex	697 (51.1)	637 (52.6)	407 (47.7)	258 (47.2)
Non-White race	51 (3.7)	69 (5.7)	40 (4.7)	30 (5.5)
High school education or less	419 (30.7)	439 (36.3)	287 (33.6)	176 (32.2)
Dementia at last clinical visit	889 (65.2)	996 (82.3)	773 (90.5)	499 (91.2)
MMSE at last visit *, Mean (SD)	19.5 (9.2)	15.7 (9.5)	13.1 (9.0)	13.3 (9.1)
APOE ε4 allele*	321 (31.5)	518 (55.5)	430 (69.4)	289 (70.0)

Abbreviations: MMSE, Mini-Mental State Examination

^{*} Number of participants missing data: MMSE = 552 (13.1%), APOE = 991 (24.9%)

Table 2

Clinical and Pathologic characteristics of subjects with and without co-occurring cerebral amyloid angiopathy (CAA) and neuritic plaques.

	No/Sparse Neuritic Plaques		Moderate/Frequent Neuritic Plaques		<i>P</i> ^{**}
	No CAA (n=565)	Any CAA (n=281)	No CAA (n=799)	Any CAA (n=2,331)	
N (%) unless otherwise noted					
Clinical Characteristics					
Age at death (years), Mean (SD)	85.4 (9.3)	87.1 (8.8)	83.0 (8.2)	82.3 (8.0)	<0.001
Female sex	281 (49.7)	131 (46.6)	416 (52.1)	1,171 (50.2)	0.46
Non-White race	25 (4.4)	19 (6.8)	26 (3.3)	120 (5.2)	0.06
High school education or less	150 (26.6)	97 (34.5)	269 (33.7)	805 (34.5)	0.004
Dementia at last clinical visit	237 (42.0)	171 (60.9)	652 (81.6)	2,097 (90.0)	<0.001
APOE ε4 allele [*]	51 (12.7)	72 (36.7)	270 (43.8)	1,165 (65.8)	<0.001
Pathologic Characteristics					
Any Hemorrhages [*]	36 (6.4)	27 (9.6)	36 (4.5)	163 (7.0)	0.02
Gross infarcts [*]	187 (33.3)	101 (36.7)	179 (22.7)	572 (24.9)	<0.001
Microinfarcts [*]	126 (22.7)	86 (32.0)	139 (17.6)	447 (19.6)	<0.001
Moderate to Severe Arteriosclerosis [*]	199 (38.3)	128 (49.2)	265 (37.5)	861 (44.1)	0.001
Subcortical leukoencephalopathy [*]	56 (10.0)	28 (10.0)	56 (7.0)	271 (11.7)	0.002
Medial temporal lobe sclerosis [*]	48 (8.6)	28 (10.1)	82 (10.4)	277 (12.1)	0.09
Neocortical Lewy bodies	64 (11.3)	47 (16.7)	143 (17.9)	357 (15.3)	0.01
Braak Stage V\VI	19 (3.4)	13 (4.6)	194 (24.3)	630 (27.0)	<0.001
Moderate/frequent Diffuse plaques [*]	90 (17.1)	117 (43.3)	574 (85.2)	1,892 (92.3)	<0.001

* Number of participants missing data: APOE = 991 (24.9%), hemorrhages = 16 (<1%), gross infarcts = 56 (1.4%), microinfarcts = 89 (2.2%), arteriosclerosis = 538 (13.5%), subcortical leukoencephalopathy = 33 (<1%), medial temporal lobe sclerosis = 59 (1.5%), and diffuse plaques = 457 (11.5%).

** Pearson χ^2 test or Fisher's exact test (if any categories included <10 subjects) were used to compare categorical measures and ANOVA was used to compare continuous measures.

Table 3

Vascular risk factors at last visit in UDS subjects with (n= 246) and without (n=281) cerebral amyloid angiopathy (CAA) in APOE ε4 negative subjects.

	No/Sparse Neuritic Plaques		Moderate/Frequent Neuritic Plaques		<i>P</i> ^{**}
	No CAA (n=140)	Any CAA (n=53)	No CAA (n=141)	Any CAA (n=193)	
	N (%) unless otherwise noted				
Clinical Characteristics [*]					
Smoking history	74 (52.9)	24 (46.2)	72 (51.8)	83 (44.2)	0.36
Hypertension	92 (66.7)	36 (67.9)	87 (61.7)	121 (62.7)	0.74
Hypercholesterolemia	71 (51.5)	22 (42.3)	67 (48.2)	92 (48.2)	0.73
Diabetes	18 (12.9)	9 (17.0)	16 (11.4)	22 (11.4)	0.71

* Number of participants missing data: Smoking = 8 (1.5%); hypertension = 2 (<1%); hypercholesterolemia = 7 (1.3%)

Table 4

Association between cognitive scores proximal to death and CAA severity (among subjects with a clinical visit within 2 years of death).^{*}

	APOE ε4 negative			APOE ε4 positive		
	β	95% CI	P	β	95% CI	P
MMSE (N=2009)						
CAA Severity						
None	---	---	---	---	---	---
Mild	-0.81	(-1.62, -0.01)	0.048	0.05	(-1.19, 1.28)	0.94
Moderate	-2.67	(-3.83, -1.50)	<0.001	-0.22	(-1.45, 1.02)	0.73
Severe	-2.26	(-3.79, -0.74)	0.004	0.15	(-1.24, 1.53)	0.84
CDR-SB[†] (N=963)						
CAA Severity						
None	---	---	---	---	---	---
Mild	-0.96	(-1.62, -0.30)	0.004	-0.11	(-1.14, 0.92)	0.84
Moderate	-1.59	(-2.64, -0.54)	0.003	-0.33	(-1.67, 1.02)	0.63
Severe	-2.15	(-4.13, -0.18)	0.03	-0.34	(-1.71, 1.02)	0.62

Abbreviations: CAA, cerebral amyloid angiopathy; CDR-SB, clinical dementia rating sum of boxes; CI, confidence interval; MMSE, mini-mental state examination

^{*} Models adjusted for age at death, education, non-white race, years between death and last visit, Braak stages, neuritic plaque score, neocortical Lewy bodies, hemorrhages, gross infarcts, microinfarcts, and medial temporal lobar sclerosis

[†] Scores have been inverted so decrease in score = lower functioning