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Cerebral Amyloid Angiopathy: Similarity in African-Americans and Caucasians with Alzheimer's Disease

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Abstract

Cerebral amyloid angiopathy (CAA) of the Aβ type is variably present in the brains of patients with Alzheimer's disease (AD). CAA contributes to cognitive decline and increases the risk of lobar hemorrhage; because both AD-typical dementia and lobar hemorrhage are more common in African-Americans than in Caucasians, we postulated that African-Americans with AD might be particularly susceptible to CAA. To test this hypothesis, we analyzed CAA histopathologically in the large vessels and capillaries of autopsy-derived frontal, temporal, parietal and occipital cortical samples from African-Americans (n=18) and Caucasians (n=19) with end-stage AD. In the combined cohort of 37 subjects, 22% of the subjects had severe CAA in large vessels, and 11% had severe CAA in capillaries. However, the prevalence and histopathologic characteristics of CAA were similar in the African-Americans and Caucasians. This conclusion was substantiated in an independent sample from the National Alzheimer's Coordinating Center database, in which the degree of CAA was comparable in 1554 Caucasians and 68 African-Americans with end-stage AD. These findings support a growing consensus that the fundamental histopathologic features of Alzheimer's disease are largely impartial to the race of the afflicted.

Keywords

Abeta; aging; amyloid; cerebrovascular amyloidosis; dementia; ethnicity; race; tauopathy; vascular disease

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INTRODUCTION

Although African-Americans are more likely than Caucasians to manifest clinically diagnosed Alzheimer's disease (AD) [1–7], the lesions that define the disease - senile (Aβ) plaques and neurofibrillary (tau) tangles - are similarly present in both groups [8, 9]. The reasons for this discrepancy are uncertain; AD is the most common form of dementia [10], but cognition can be seriously compromised in at least 50 other medical conditions [11], many of which may interact with AD-type pathology to advance symptom onset or accelerate decline [12, 13]. Ethnoracial differences in the dementia phenotype thus might reflect the influence of factors that differentially modulate or unmask the concurrent pathobiology of AD. Of these, vascular disease is a frequent co-morbid condition [14], and the presence of vascular risk factors in mid-life is associated with increased brain Aβ deposition [15] and dementia [16] in old age.

Aging African-Americans are at a relatively high risk of developing cardiovascular and metabolic disorders[17–19] as well as mixed pathologies in the brain, particularly plaques and tangles along with α-synucleinopathy (Lewy body disease) and/or infarcts[7, 20]. The contribution of cardiovascular disease to dementia has received special attention because African-Americans are especially susceptible to hypertension[19], diabetes/metabolic disorder[1, 5, 21, 22], cerebrovascular disease[7] and stroke[23–25]. Since ethnoracial differences might reflect disparities in modifiable risk factors, it is important to define the underlying pathobiology in differentially vulnerable populations.

Of particular interest is the elevated predisposition of older African-Americans to lobar hemorrhage[25], a disorder that has been linked to cerebral amyloid angiopathy (CAA)[26, 27]. Neuropathologically, CAA is characterized by the deposition of amyloid in and around the walls of cerebral blood vessels[28–30]. Several different proteins are capable of forming cerebrovascular amyloid[29], but in AD, the culpable protein is Aβ, typically a 40- or 42-amino acid cleavage product of the Aβ-precursor protein that also constitutes the cores of senile plaques[31]. Amyloid impairs the integrity of the vascular wall and increases the likelihood that affected vessels will rupture[31]. CAA also is thought to be related to diminished drainage of cerebrospinal fluid along perivascular pathways, a mechanism by which the brain eliminates toxins and waste[32]. CAA contributes to cognitive decline[33–40], and it has been associated with cortical atrophy[41] and disruption of the cerebral connectome[42]. In AD, CAA most often afflicts arterioles coursing through the leptomeninges and parenchyma of the brain; veins and capillaries are less often affected[29, 39], but when present, capillary CAA appears to have distinctive pathobiologic features[43].

Although CAA occurs to some extent in nearly all AD patients[44–46], the level of involvement varies widely, and it is considered severe in approximately 20% of cases[27, 32, 47, 48]. An earlier study provided suggestive evidence that CAA might be more common in African-Americans than in white individuals[9], but the difference between the groups was not statistically significant, and the prevalence of CAA in the white subjects was lower than expected based on the prior literature[9]. A more recent investigation of a larger cohort of subjects with dementia also indicated that CAA is more often present in African-Americans [7]. However, the sample of African-Americans also had a higher prevalence of AD-type

lesions, and the severity of CAA was not assessed, leaving open the question of whether CAA differs in African-Americans with advanced AD. In light of the elevated incidence and prevalence of clinical AD[1–5, 7] and lobar hemorrhage[25] among African-Americans, along with the established link between lobar hemorrhage and CAA[31], we sought to test the hypothesis that African-Americans with AD are particularly susceptible to CAA, and that this vulnerability contributes to their elevated predisposition to dementia. Our findings instead indicate that both the prevalence and phenotype of CAA are similar in African-Americans and Caucasians with end-stage AD.

MATERIALS AND METHODS

Subjects

Thirty-seven patients who self-identified (or were identified by their family members) as African-American (n = 18; 12 females, 6 males) or non-Hispanic Caucasian (n = 19; 14 females, 5 males) served as subjects. Brains were collected at autopsy during the years spanning 2003 to 2014 at the Emory University Alzheimer's Disease Research Center (ADRC) in Atlanta, Georgia. The two ethnoracial groups were matched as closely as possible in terms of age at death, duration of disease, postmortem interval (PMI), ApoE type, sex, and level of education (Table 1); however, the prevalence of hypertension was greater in the African-Americans than in the Caucasians (see Table 1 and the Discussion). In a supplementary analysis, we compared the degree of CAA in 1554 Caucasians and 68 African-Americans with clinically diagnosed and histopathologically confirmed advanced Alzheimer's disease (Table 3) in a multi-institutional dataset from the National Alzheimer's Coordinating Center (NACC) (for details, see https://www.alz.washington.edu/). To ensure independence from our primary cohort (above), this analysis excluded data from subjects furnished to NACC by Emory (a contributing institution). Note that this sample of subjects partially overlaps with the NACC sample analyzed by Graff-Radford et al. [7], except that our analysis concentrated only on those with definite advanced AD, and we evaluated the degree of CAA instead of just its presence or absence. Data specifically on capillary CAA were not available for the NACC subjects. This study was conducted under the auspices of the Emory ADRC and was approved by the Emory Institutional Review Board. Informed consent was obtained from all subjects or their family members.

Histopathology and Quantitation of CAA

The brains were immersion-fixed for 1–2 weeks in phosphate-buffered, 4% (w/v) de-polymerized paraformaldehyde. For histopathological diagnosis and staging of the cases, tissue blocks from multiple brain areas were embedded in paraffin, cut at 8 μm thickness, and sections stained with hematoxylin and eosin, the Bielschowsky silver stain, and immunohistochemically labeled with antibodies to Aβ (4G8; Biolegend, San Diego, CA), tau (PHF-1; courtesy of Peter Davies, The Feinstein Institute for Medical Research), TDP-43 (Cosmo Bio USA, Carlsbad, CA), ubiquitin (Millipore, Temecula, CA), and α-synuclein (Wako, Mountain View, CA). In all subjects, Thal phases of Aβ-proteopathy[49], Braak stages of tauopathy[50], CERAD neuritic plaque scores[51], and the combined Aβ (**A**myloid), **B**raak and **C**ERAD (ABC) scores for the degree of AD-type neuropathology[52]

were determined; the presence of comorbid brain conditions also was noted (summarized in Table 2).

Aβ-CAA was assessed in four distinct neocortical regions: the frontal lobe (primarily Brodmann area 8), temporal lobe (primarily Brodmann areas 21/22), parietal lobe (Brodmann area 7) and occipital lobe (primarily Brodmann areas 17/18). Aβ-immunostained tissue sections from each of the four regions were examined independently by two investigators (DMK and LCW) who were incognizant of the ethnoracial and other characteristics of the subjects. The prevalence of CAA in all large vessels (arteriolar and venous; lvCAA) was determined in both the brain parenchyma and the superficial vessels of the leptomeninges; in addition, the degree of CAA in parenchymal capillaries (vessels of apparent diameter of ~10 μm; capCAA) was evaluated. Using a modified quantitative scale similar to that of Olichney et al.[48, 53], each type of CAA was assigned a score of 0 (none) to 5 (most severe) in each brain area. The CAA scores were standardized by comparison to a prepared set of photographs illustrating the different levels of involvement, with half-step intermediate scores (1.5, 2.5, etc.) permitted. In cases where three or fewer positive vessels were evident in a given tissue section, a score of 0.5 was assigned. By *a priori* agreement of the two raters, cortical regions with CAA scores of 0 to 1.0 were considered to have no-to-light CAA, regions with scores of >1.0 to 2.0 were considered to have moderate CAA, and regions with scores >2.0 were considered to have severe CAA. The expanded scale in the severe range (>2.0 to 5.0) allowed us to capture the full breadth of severity in the context of spatial variation in the extent of CAA within a given sample. Cohen's kappa coefficient indicated satisfactory inter-rater concordance in assignment of categorical severity levels (none-light, moderate, or severe) for lvCAA (kappa = 0.91) and capCAA (kappa = 0.70), so the means of the two raters' scores were calculated as the reported values. Final lvCAA and capCAA scores then were assigned to each brain area of all 37 cases.

Statistical Analysis

In the primary cohort at Emory, patient characteristics were compared using the two-sample *t*-test for continuous variables, or, for categorical variables, the Chi-square test or Fisher's exact test. Because the scores for lvCAA and capCAA were not normally distributed, the Wilcoxon rank-sum test was used to compare the scores between the ethnoracial groups, genders, *APOEε4* carriers/non-carriers, *APOEε4* homozygotes/heterozygotes, presence of hypertension, and the quartiles of age at death and duration of disease. Spearman's rank correlation coefficient (rho) was used to evaluate correlations involving lvCAA and capCAA.

In the supplemental dataset from NACC, age at death, disease duration, and education level were analyzed using two-sample *t*-tests assuming equal variances. Owing to dissimilar variances, a *t*-test assuming unequal variances was used to assess PMIs in the two groups. Gender, *APOEε4* status and the presence or absence of hypertension where analyzed by Chi-square. The degree of CAA (ranked by evaluators at the NACC-contributing institutions) was assessed by comparing the distribution of the 4 scores (0,1,2,3) in African-American and Caucasian subjects using the Chi-square test.

RESULTS

General Findings in the Unified Emory Cohort

Diagnostic neuropathologic findings—All 37 subjects in the Emory cohort had CERAD neuritic plaque scores and Thal Aβ plaque levels indicative of a neuropathologic diagnosis of AD (Table 2). With the exception of case AD6 (Braak stage III), the cases also exhibited marked tau deposition in the frontal, temporal and parietal cortices, with more variable deposition in the occipital cortex, consistent with Braak tauopathy stages V and VI (Table 2).

Distribution of CAA—In the 37 subjects as a whole, CAA was most prominent in the occipital lobe, in agreement with the findings of others[30, 54–56]. The mean overall scores (rounded to the nearest tenth) for lvCAA were 1.5 (occipital), 1.2 (parietal), 1.1 (temporal), and 1.2 (frontal); for cap CAA the scores were 1.1 (occipital), 0.6 (parietal), 0.3 (temporal) and 0.4 (frontal).

Large-vessel CAA—The mean scores for parenchymal lvCAA correlated strongly with the mean scores for leptomeningeal lvCAA (rho = 0.86, $p < 0.001$); these scores therefore were combined into a single mean lvCAA score for each brain area in each subject. The degree of lvCAA varied among the subjects, with the lvCAA scores in the total cohort skewing toward light-to-moderate involvement. Specifically, the mean composite lvCAA scores (i.e., the mean of the scores for all 4 cortical regions) were less than 2 (light-to-moderate) in 29 of the cases (78%) and greater than 2 (severe) in 8 cases (22%) (Table 2). Within subjects, the lvCAA scores correlated significantly across the 4 cortical regions (rho = 0.81, $p < 0.001$); for this reason, and because of the sometimes patchy distribution of CAA within the cortex[55], the mean of the lvCAA scores for the 4 cortical regions was used for subsequent analyses. The extent of lvCAA was not significantly related to age at death, duration of disease, sex of the subjects, presence of hypertension, or *APOEε4* positivity, although there was a trend toward greater lvCAA in *APOEε4/4* cases than in *APOEε3/4* cases (Wilcoxon rank-sum test, $p = 0.09$). Four cases (two African-Americans and two Caucasians) presented pronounced dyshoric lvCAA, a condition in which the Aβ deposition extends beyond the vascular wall into the surrounding parenchyma (Figures 1A,B; 2). One other case (a Caucasian) had conspicuous dyshoric lvCAA only in the occipital cortical sample. In all of these instances, the dyshoric vessels often were surrounded by profuse tau-immunoreactive processes that spatially overlapped with the perivascular Aβ (Figure 2). Diffuse CAA-related inflammation/angiitis[30] was not seen in any of the subjects.

Capillary CAA—Capillary CAA was less prevalent than was large-vessel CAA in the overall Emory cohort. Fourteen subjects had no detectable capCAA, 19 had light-to-moderate capCAA (all had mean scores of 1.3 or less), and 4 had severe capCAA (scores of 2.3, 3.0, 3.9 and 5.0) (Table 2). As with lvCAA, the capCAA scores correlated significantly across the 4 cortical regions (rho = 0.77, $p < 0.001$), so the mean capCAA scores across the 4 sites was used as the representative value for further analysis. The degree of capCAA was not significantly related to duration of disease, age at death, or presence of hypertension, but males tended to have more capCAA than females (Wilcoxon rank-sum test, $p = 0.054$);

capCAA also tended to be more abundant in *APOEε4*-positive subjects, although the difference from *APOEε4*-negative subjects was not statistically significant (Wilcoxon rank-sum test, $p = 0.25$). Of the 7 moderate-to-severe capCAA cases, 4 were *APOEε4/4*-homozygous, and 3 were *APOEε3/4*-heterozygous. Because of the relatively small proportion of males (30%) as well as *APOEε3/3*- and *APOEε4/4*-bearing subjects (22% and 25%, respectively) in the inclusive cohort, comparisons of the genders and *APOE* groups here should be interpreted cautiously. In agreement with other reports[43, 57], the presence of copious capCAA in a given sub-region of cortex was associated with sparse parenchymal Aβ plaques within the same space (Figure 1 C,D). Dyshoric capCAA sometimes was associated with peri-capillary tau-immunoreactive processes (not shown). The degree of capCAA in the total cohort showed a trend toward correlation with the degree of lvCAA (rho = 0.32, $p = 0.057$). While severe capCAA was present only in patients with moderate-to-severe lvCAA, several cases of moderate-to-severe lvCAA had little or no capCAA (Table 2).

CAA in African-Americans and Caucasians with AD

Emory cohort—The amount of CAA in the 37 Emory subjects did not differ significantly between African-Americans and Caucasians (lvCAA: Wilcoxon rank-sum test, $p = 0.94$; capCAA: Wilcoxon rank-sum test, $p = 0.13$) (Figures 1–3). Large-vessel CAA was severe (mean lvCAA scores above 2.0) in 4 subjects in each ethnoracial group (22% of African-Americans and 21% of Caucasians). Capillary CAA was severe in 3 African-Americans (17%) and in 1 Caucasian (5%) (Table 2 and Figure 3).

Comorbid brain conditions were slightly more common in the African-American group (30 comorbidities in 18 subjects) than in the Caucasian group (25 comorbidities in 19 subjects) (Table 2). Of these, only the proportion of patients with Lewy body disease trended toward a difference between African-Americans (72%) and Caucasians (42%) (Chi-square = 3.3, $p = 0.07$). Five of the 18 African-Americans had evidence of infarcts, as did 3 of 19 Caucasians (Fisher's Exact Test, $p = 0.45$). Of the 31 subjects for which sufficient clinical data were available, the proportion of African-Americans with hypertension (14/16: 88%) was significantly greater than in Caucasians (2/15: 13%) (Fisher's Exact Test, $p < 0.001$). However, in the combined Emory cohort, the presence of hypertension was not significantly related to the degree of lvCAA ($p = 0.62$) or capCAA ($p = 0.38$) (Table 2).

NACC cohort—To further assess the degree of CAA in the two ethnoracial groups, we evaluated data from a large, independent sample of subjects (1554 Caucasians and 68 African-Americans) with clinicopathologically confirmed AD from the NACC database (Table 3). In the combined NACC cohort, CAA was severe (score of 3 on a scale of 0–3) in 18% of the NACC subjects. Unlike the Emory cohort (in which the two ethnoracial groups were deliberately matched on several variables), the proportion of males and females differed significantly in the Caucasian and African-American NACC groups, and mean educational attainment was significantly greater in Caucasians (Table 3). Similar to the Emory cohort, African-Americans in the NACC cohort were significantly more likely to have been diagnosed with hypertension during life (Chi-square = 20.35, $p < 0.001$); however,

the distribution of CAA scores did not differ significantly in the two groups (Chi-square = 2.72, $p = 0.44$) (Table 4).

DISCUSSION

Despite a relatively high incidence of AD-type dementia[1–5, 7] and lobar hemorrhage[25], African-Americans with AD appear not to be disproportionately vulnerable to cerebral β-amyloid angiopathy. This finding supports the conclusions of Wilkins et al.[9] and Riudavets et al.[8], and indicates that CAA does not contribute significantly to the differential susceptibility to AD among aging African-Americans.

Older AD patients in general are more likely than younger patients to manifest comorbid brain disorders such as α-synucleinopathy and microinfarcts[7, 58], and such mixed brain pathologies have been reported to be more common in blacks than whites with clinical AD[20]. In our primary cohort of 37 subjects, the prevalence of comorbidities was slightly higher among African-Americans (30 comorbidities in 18 subjects) compared to Caucasians (25 comorbidities in 19 subjects). In particular, African-Americans tended to have more α-synucleinopathy than did Caucasians, consistent with previous investigations[7, 20]. Several systemic risk factors for age-associated cognitive decline also are more prevalent among African-Americans, such as cardiovascular and metabolic disorders[17, 18], including hypertension[19]; as expected, more African-American subjects in both the Emory and NACC cohorts had been diagnosed with hypertension than had Caucasians, although both groups had similar levels of CAA. It is therefore plausible that the deleterious effects of Aβ- and tau-accumulation on brain function are more likely to be unmasked by comorbid conditions in African-Americans, thereby increasing the probability of dementia. Imaging of cerebral β-amyloid in living subjects using florbetapir positron-emission tomography has indicated that older, cognitively normal African-Americans have a greater Aβ burden than a comparable sample of whites[59]. Longitudinal studies employing brain imaging and/or sensitive biomarkers for AD and comorbid conditions in living patients are needed to more fully evaluate the contribution of comorbidity to cognitive deterioration in differentially vulnerable populations.

Large vessel CAA was severe in approximately one-fifth of the subjects in both the Emory and NACC combined cohorts of African-Americans and Caucasians, in agreement with previous analyses[27, 32, 47, 48, 60]. We also confirm[29, 39] that CAA is less common in capillaries than in large vessels (11% of the Emory subjects had severe capCAA, and 38% had none). Severe capCAA was present only in patients with moderate-to-severe lvCAA, although many cases of moderate-to-severe lvCAA had little capCAA (Table 2). There was a tendency for African-Americans to have more capCAA (Figure 3), an observation that warrants further study in a larger group of subjects. In addition, all subjects were analyzed at the end-stage of AD; whether the prevalence of CAA differs in the two groups at earlier stages of pathogenesis remains unknown. It will also be important to determine if CAA in the absence of AD lesions is more common in different ethnoracial groups.

Earlier reports have noted that regions of severe capillary CAA tend to have few parenchymal Aβ plaques in the same space[43, 57], and our observations confirm this

(Figure 1C,D). Extant evidence thus suggests that the deposition of Aβ in capillaries may involve a mechanism that differs from that in large vessels and plaques, possibly with different functional consequences for the brain[43]. The degree of capCAA can be strongly associated with dementia in AD[61], and dyshoric capCAA has in some instances been linked to pericapillary inflammation and a rapidly progressive form of dementia[62]. Pericapillary inflammation was not evident in any of the 37 subjects in which the degree of capCAA was specifically investigated.

The *APOEε4* allele is associated with an increased risk of both AD[63–65] and CAA[56, 66], and the *ε4* allele has been reported to be more common in African-Americans than Caucasians with dementia[7]. In the present primary sample of 37 subjects (in which the presence of *APOEε4* was roughly matched in the two ethnoracial groups), moderate-to-severe capCAA was found only in *APOEε4*-bearing subjects, confirming previous findings[43, 67]; although lvCAA was more abundant in *APOEε4*-bearing subjects compared to those lacking *APOEε4*, the group difference did not reach statistical significance, possibly owing to the relatively small percentage of *APOEε4*-negative subjects (22%) in this sample. In addition, the effect of the *APOEε4* allele on CAA risk has been reported to be greater for males than for females[8], and most of the subjects that we analyzed (70%) were females. In the context of previous observations [56, 66], our results generally substantiate the importance of *APOEε4* as a genetic risk factor for CAA.

A prior analysis of two *APOEε4/4* homozygotes with severe CAA described marked perivascular neuritic tauopathy associated with dyshoric Aβ deposition[68]. We also found profuse tau-immunoreactive processes surrounding dyshoric amyloidotic vessels, but this was seen both in *APOEε3/3*- and *APOEε3/4*-bearing subjects (Figure 2). Interestingly, the spatial distribution of the tauopathic neurites overlapped considerably with that of the perivascular Aβ, and in cases of severe non-dyshoric CAA, little perivascular tauopathy was evident. The region of tau and Aβ co-deposition around dyshoric vessels thus could yield profitable insights into how the two proteins interact in the AD brain.

We matched the two ethnoracial groups in the Emory sample as closely as possible on a number of variables, although there is unavoidable selection bias in autopsy-based studies[58], and willingness to undergo autopsy is subject to cultural differences[69–71]. In addition, both ‘African-American’ and ‘Caucasian’ are broad terms that include people from diverse geographic and cultural backgrounds[1, 72]. Even among people of African origin, dementia has been noted to be significantly more common in African-Americans living in Indianapolis than in age-matched Africans in Ibadan, Nigeria[73]. The causes of this disparity are unclear[1], but the findings emphasize the potential pitfalls that attend the multifaceted concept of race[74]. In addition, it is likely that the pathobiology of dementia is influenced by social and environmental factors that differ among different ethnoracial populations[75]. To the extent that ethnoracial differences in the vulnerability to certain disease processes can be characterized, it may be possible to identify group-specific, modifiable risk factors that can be targeted to reduce the burden of disease[7]. Of these, cardiovascular and metabolic risk factors should command special attention.

We conclude that both the degree and type of cerebrovascular Aβ deposition are largely similar in African-Americans and Caucasians with end-stage AD. This finding underscores the overall pathologic similarity of AD-type lesions in these groups[8, 9, 76], and supports the broader view that, despite the normal inter-individual heterogeneity in the disease phenotype[77], the fundamental neuropathologic features of AD are comparable in humans of differing ethnoracial backgrounds.

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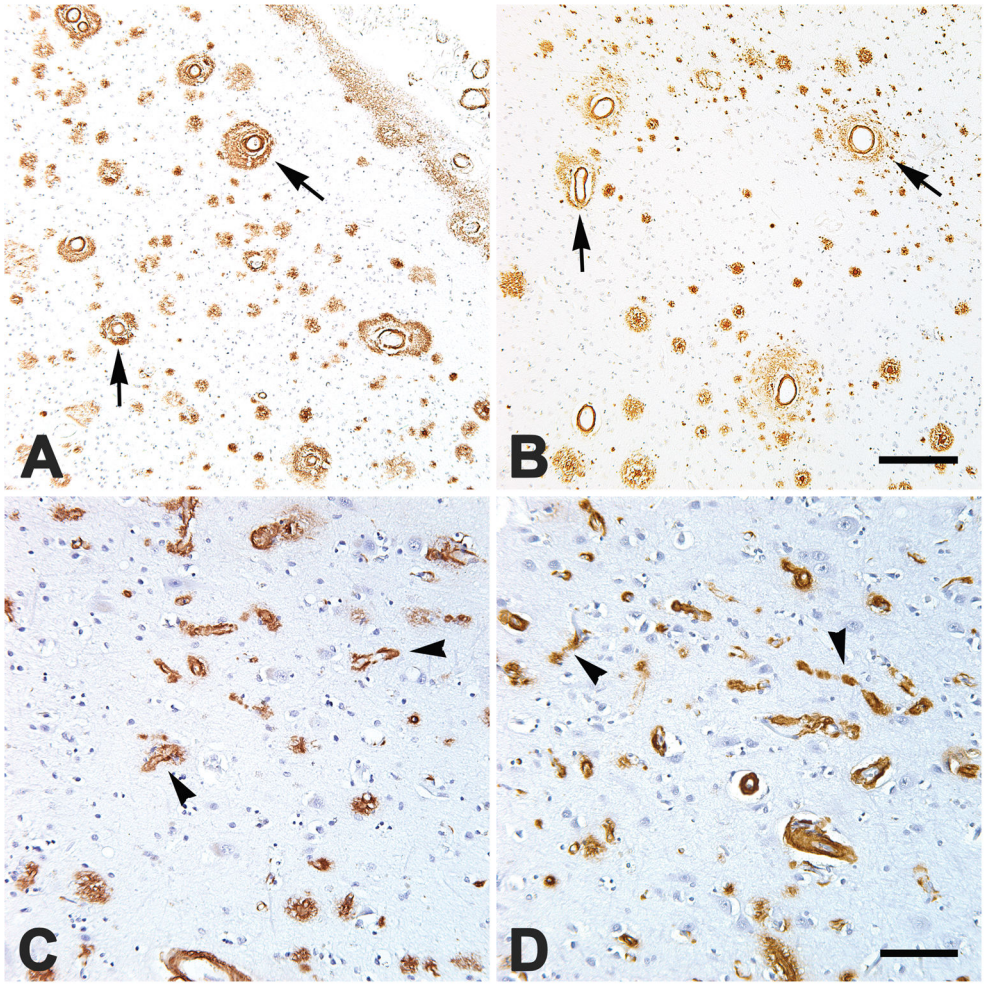

FIGURE 1.

Severe, dyshoric large-vessel CAA (**A**,**B**; four vessels are marked by arrows) in occipital (**A**) and parietal (**B**) neocortical sections, and severe dyshoric capillary CAA (**C**,**D**; four are marked by arrowheads) in the parietal neocortices of two African-Americans (**A**,**C**) and two Caucasians (**B**,**D**). Areas of heavy capCAA generally had relatively few parenchymal Aβ plaques (**C**,**D**). Nissl counterstain. Scale bar in **B** = 200 μm for **A**&**B**, scale bar in **D** = 100 μm for **C**&**D**.

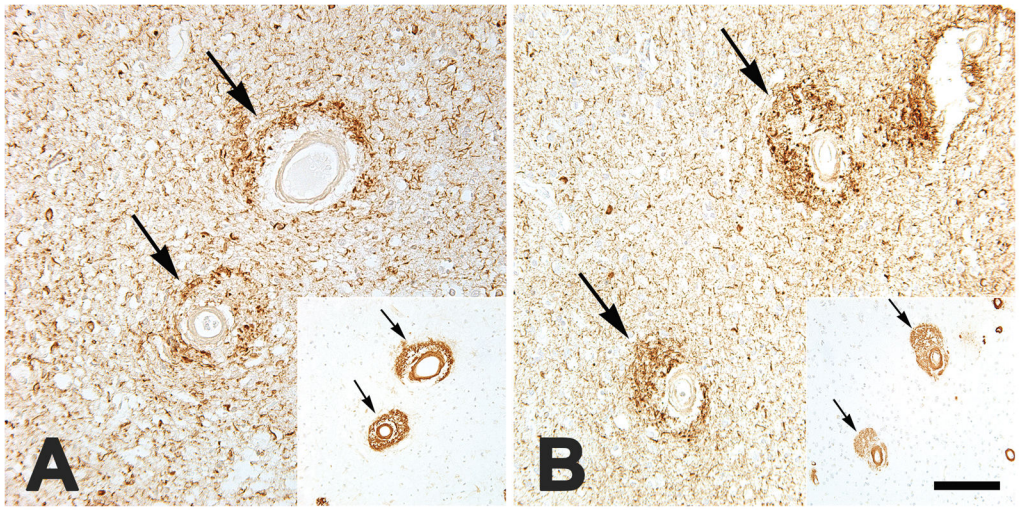

FIGURE 2.

Large cortical blood vessels with dyshoric CAA are surrounded by profuse neuritic tauopathy (antibody PHF-1), here shown in the parietal neocortex of an APOEe3/4-bearing African-American man (AD7; **A**) and the occipital neocortex of an APOEe3/3-bearing Caucasian woman (AD27; **B**). Insets show intramural and perivascular Aβ immunoreactivity in the same vessels in nearby tissue sections (antibody 4G8). Note the spatial overlap of tauopathic neurites and perivascular Aβ. Nissl counterstain. Bar = 200 μm for the insets, and 80 μm for the main panels.

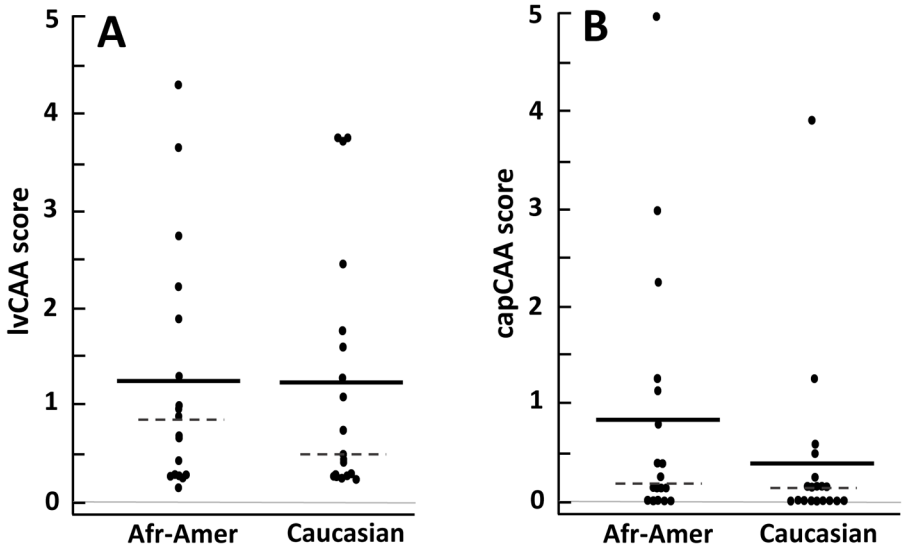

FIGURE 3.

Distribution of CAA scores in 18 African-American (Afr-Amer) and 19 Caucasian subjects. Each dot represents the mean score of the 4 brain regions for lvCAA (**A**) and capCAA (**B**) in each subject. The group means are indicated by the solid bars, and the medians by the dashed lines. There were no statistically significant differences in the amount of lvCAA (p = 0.94) or capCAA (p = 0.13) between the two ethnoracial groups.

TABLE 1

Characteristics of African-Americans and Caucasians in the Emory cohort of 37 subjects with clinically diagnosed and pathologically confirmed AD.

Variable	African-Americans (*n*=18)	Caucasians (*n*=19)	*p* value
Age at death (yrs)[+]	73.8 ± 12.4	75.1 ± 10.4	0.75[ǂ]
Duration (yrs)[+^]	9.4 ± 4.2	10.8 ± 4.1	0.34[ǂ]
PMI (hrs)[+]	17.6 ± 13.0	12.2 ± 6.8	0.12[ǂ]
Gender *n* (%)			0.64[ǂ]
Male	6 (33%)	5 (26%)	
Female	12 (67%)	14 (74%)	
APOE genotype *n* (%)[^^]			
ε4/4	6 (33%)	3 (17%)	
ε3/4	8 (44%)	10 (56%)	
ε3/3	4 (22%)	4 (22%)	
ε2/4	0	1 (6%)	
APOEε4-positive *n* (%)[^^]			0.61[ǂ]
Yes	14 (78%)	14 (78%)	
No	4 (22%)	4 (22%)	
Hypertension *n* (%)[‡‡]	14/16 (88%)	2/15 (13%)	**<0.001**
Education (yrs)[§]	14.6 ± 3.3	14.9 ± 2.4	0.77[ǂ]

All percentages are rounded to the nearest whole number

APOE: apolipoprotein E

PMI: postmortem interval

[+] Mean ± standard deviation

[^] Time from diagnosis to death; Data not available for 2 Caucasians

[^^] Data not available for 1 Caucasian

[‡‡] Data not available for 2 African-Americans and 4 Caucasians

[§] Data not available for 6 African-Americans and 6 Caucasians

[ǂ] Statistically non-significant

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TABLE 2

CAA scores (overall mean scores based on a scale of 0–5), neuropathologic stages, secondary (2º) neuropathologic diagnoses, and prior hypertension for subjects in the Emory cohort. African-Americans are denoted by §.

Subject	lvCAA	capCAA	Thal	Braak	CERAD	ABC	2º NP Diagnoses	Hyperten
AD1 §	1.1	0	5	VI	C	high	LBD	Yes
AD2 §	0.4	0.4	5	VI	C	high	TDP, meningioma, HV	No
AD3 §	0.2	0.1	5	V	C	high	LBD, TDP	*nd*
AD4 §	0.3	0.4	5	VI	C	high	LBD, sm infarcts	Yes
AD5 §	1.3	0.3	5	VI	C	high		Yes
AD6 §	1.0	0.8	4	III	C	intermed	LBD	Yes
AD7 §	4.3	3.0	5	VI	C	high	TDP, LBD	Yes
AD8 §	1.9	2.3	4	VI	C	high	LBD, sm infarcts	Yes
AD9 §	2.2	0.1	5	VI	C	high		No
AD10 §	0.9	0	5	VI	C	high		Yes
AD11 §	0.7	1.1	5	VI	C	high	LBD, sm infarcts	*nd*
AD12 §	3.6	5.0	4	VI	C	high	LBD, TDP, TL scler	Yes
AD13 §	0.5	0	5	V	C	high	sm-med infarcts, TDP, LBD	Yes
AD14 §	0.3	0	4	V	C	high	LBD, TDP, sm-med infarcts	Yes
AD15 §	0.3	0	5	VI	C	high	LBD	Yes
AD16 §	0.8	0.1	5	VI	C	high	TL scler, TDP	Yes
AD17 §	2.6	1.3	5	VI	C	high	meningitis, LBD	Yes
AD18 §	0.3	0.1	5	VI	C	high	LBD	No
AD19	0.3	0	5	VI	C	high		No
AD20	0.3	0.5	5	VI	C	high		No
AD21	0.3	0.3	5	VI	C	high	LBD, TDP	No
AD22	0.3	0.1	5	VI	C	high	TDP	*nd*
AD23	0.2	0.6	5	V	C	high	LBD	No
AD24	1.0	0.1	5	VI	C	high	LBD	*nd*

Subject	lvCAA	capCAA	Thal	Braak	CERAD	ABC	2º NP Diagnoses	Hyperten
AD25	0.4	0	5	VI	C	high		No
AD26	0.5	0	5	VI	C	high		No
AD27	3.7	0.1	5	VI	C	high	TDP	No
AD28	1.8	1.3	4	V	C	high	TL scler, TDP	Yes
AD29	0.5	0	5	V	C	high	LBD, TDP	*nd*
AD30	1.6	0	5	VI	C	high	TL scler, TDP, LBD, sm infarcts	*nd*
AD31	3.7	0.1	5	VI	C	high		No
AD32	3.8	3.9	4	VI	C	high	sm infarcts	No
AD33	1.3	0	5	VI	C	high	med-large infarcts	No
AD34	0.7	0	5	VI	C	high	LBD, TDP	No
AD35	2.5	0	5	VI	C	high	sm-med infarcts, TDP	No
AD36	0.3	0	5	V	C	high	LBD, TDP, arterioscl (severe)	Yes
AD37	0.5	0.1	5	VI	C	high	LBD, TDP	No

ABC: Amyloid-Braak-CERAD neuropathology score; arterioscl: arteriosclerosis; CERAD: Consortium to Establish a Registry for Alzheimer's Disease (pathology); Hyperten: hypertension; HV: Hypertensive Vasculopathy; intermed: intermediate; LBD: Lewy Body Disease; *nd*: no data; sm: small; med: medium; TDP: TAR-DNA-binding protein 43KDa (TDP-43); TL scler - Temporal Lobe sclerosis

TABLE 3

Characteristics of African-Americans and Caucasians in the NACC cohort of 1622 subjects with clinically diagnosed and pathologically confirmed AD.

Variable	African-Americans (*n*=68)	Caucasians (*n*=1554)	*p* value
Age at death (yrs)[+]	81.9 ± 9.5	79.9 ± 10.5	0.13[‡]
Duration (yrs)[+,^]	10.5 ± 4.0	10.3 ± 4.0	0.62[‡]
PMI (hrs)[+,^^]	16.4 ± 18.2	11.7 ± 10.2	0.21[‡]
Gender *n* (%)			**0.02**
Male	27 (40%)	838 (54%)	
Female	41 (60%)	716 (46%)	
APOE genotype *n* (%)[^^^]			
ε4/4	11 (20%)	205 (15%)	
ε3/4	24 (44%)	597 (43%)	
ε3/3	14 (26%)	488 (35%)	
ε2/4	1 (2%)	46 (3%)	
ε2/3	4 (7%)	43 (3%)	
ε2/2	0 (0%)	2 (0.1%)	
APOEε4-positive *n* (%)[^^^]			0.44[‡]
Yes	36 (67%)	848 (61%)	
No	18 (33%)	533 (39%)	
Hypertension *n* (%)[¶]	51/62 (82%)	753/1418 (53%)	**<0.001**
Education (yrs)[+,¶¶]	13.4 ± 3.4	15.3 ± 2.9	**<0.001**

All percentages except *ε2/2* incidence in Caucasians are rounded to the nearest whole number

APOE: apolipoprotein E

PMI: postmortem interval

[+] Mean ± standard deviation

[^] Time from diagnosis to death; Data not available for 1 African-American and 13 Caucasians

[^^] Data not available for 43 African-Americans and 950 Caucasians

[^^^] Data not available for 14 African-Americans and 173 Caucasians

[¶] Data not available for 6 African-Americans and 136 Caucasians

[¶¶] Data not available for 1 African-American and 13 Caucasians

[‡] Statistically non-significant

TABLE 4

Degree of CAA (on a scale of 0–3) in African-Americans and Caucasians in the NACC cohort who were clinically diagnosed and pathologically confirmed to have AD. The frequency of CAA scores did not differ significantly between the two groups (Chi-square = 2.72, $p = 0.44$).

Group	CAA Score (*n*, %*)				Total (*n*)
	0	1	2	3	
African-Americans	13 (19%)	23 (34%)	24 (35%)	8 (12%)	**68**
Caucasians	313 (20%)	527 (34%)	434 (28%)	280 (18%)	**1554**

* Percentages are rounded to the nearest whole number