White matter atrophy in cerebral amyloid angiopathy

Panagiotis Fotiadis, BSc, Yael D. Reijmer, PhD, Susanne J. Van Veluw, PhD, Sergi Martinez-Ramirez, MD, Fikret Isik Karahanoglu, PhD, Elif Gokcal, MD, Kristin M. Schwab, BA, on behalf of the Alzheimer's Disease Neuroimaging Initiative study group, Joshua N. Goldstein, MD, PhD, Jonathan Rosand, MD, MSc, Anand Viswanathan, MD, PhD, Steven M. Greenberg, MD, PhD,* and M. Edip Gurol, MD, MSc*

Correspondence
Dr. Gurol
edip@mail.harvard.edu

Abstract

Objective

We postulated that cerebral amyloid angiopathy (CAA) is associated with white matter atrophy (WMA) and that WMA can be related to cognitive changes in CAA.

Methods

White matter volume expressed as percent of intracranial volume (pWMV) of prospectively enrolled patients without dementia diagnosed with probable CAA was compared to age-matched healthy controls (HC) and patients with Alzheimer disease (AD). Cognitive scores were also sought to understand the potential effects of WMA on cognitive function.

Results

Patients with CAA (n = 72) had significantly lower pWMV (27.97% ± 2.63) when compared to age-matched HC (n = 72; mean difference [MD], 2.38%; $p < 0.0001$) and patients with AD (n = 72; MD, 1.57%; $p < 0.0001$). Differences were most pronounced in the posterior occipital regions in both comparisons. When comparisons were restricted to groups of patients with CAA but no intracerebral hemorrhage (n = 32) or hypertension (n = 32), and age-matched HC and AD, the significant differences were unaltered. Within the CAA cohort, higher age, lobar microbleed counts, and presence of hypertension were associated with lower pWMV ($p = 0.0007$, $p = 0.031$, and $p = 0.003$, respectively). All associations remained independent in multivariable analyses. Within the CAA cohort, higher pWMV independently correlated with better scores of executive function.

Conclusions

Patients with CAA show WMA when compared to age-matched HC and patients with AD. WMA independently correlates with the number of lobar microbleeds, a marker of CAA severity. Consistent spatial patterns of WMA especially in posterior regions might be related to CAA. The association between WMA and measures of executive function suggests that WMA might represent an important mediator of CAA-related neurologic dysfunction.

Glossary

AD = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **CAA** = cerebral amyloid angiopathy; **CMB** = cerebral microbleed; **eTIV** = estimated total intracranial volume; **FLAIR** = fluid-attenuated inversion recovery; **GLM** = general linear model; **HC** = healthy control; **ICH** = intracerebral hemorrhage; **pGMV** = percent of intracranial gray matter volume; **pWMV** = percent of intracranial white matter volume; **SWI** = susceptibility-weighted imaging; **WMA** = white matter atrophy; **WMH** = white matter hyperintensity; **WMV** = white matter volume.

Cerebral amyloid angiopathy (CAA) is characterized by the accumulation of β-amyloid proteins in the walls of small and medium-sized leptomeningeal and cortical vessels resulting in a characteristic acellular wall thickening.[1,2] This vascular pathology can result in hemorrhagic lesions such as spontaneous lobar intracerebral hemorrhage (ICH) and cortical cerebral microbleeds (CMB), through breakdown of the wall, as well as ischemic consequences, such as white matter disease, because of the associated vascular dysfunction.[3–5] Multiple lines of evidence show that CAA is also associated with cognitive impairment, especially in the form of executive dysfunction, independent of acute pathologies such as lobar hemorrhages.[5–9]

Brain atrophy correlates with age and is tightly linked to dementia.[10] A recent study showed that vascular amyloid is an independent contributor to cortical atrophy, an association mostly mediated by vascular dysfunction, both in patients with a hereditary type of CAA without Alzheimer pathology as well as in older patients with sporadic CAA.[11] Despite the well-known associations between CAA and white matter pathologies such as leukoaraiosis and microstructural damage, the effects of CAA on white matter volume (WMV) are unknown.

We hypothesized that WMV expressed as percent of total intracranial white matter volume (pWMV) would be lower in CAA when compared to both age-matched healthy controls (HCs) and patients with AD. We also hypothesized that decreases in pWMV would correlate with imaging (CMB counts) and genetic (presence of *APOE* ε4) markers of CAA severity as well as executive function changes, the most characteristic cognitive manifestation of CAA.

Methods

Study design and participants
Individuals with sporadic CAA were enrolled at Massachusetts General Hospital, Boston, between March 15, 2006, and November 2, 2015. None had dementia and all carried a diagnosis of probable CAA according to the pathologically validated Boston criteria[12]; the details of enrollment into this study were published in a recent article.[11] Patients with CAA without ICH are enrolled based on finding of strictly lobar microbleeds during the workup for focal neurologic symptoms, seizures, and cognitive/gait symptoms, after ruling out dementia, other neurodegenerative diseases, and stroke. Patients with sporadic CAA without dementia (n = 72) were age-matched to HCs (n = 72) as well as patients with Alzheimer disease (AD) (n = 72);

the latter 2 cohorts were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Inclusion criteria for the ADNI study have been described extensively.[13] Participants enrolled from the ADNI cohort were selected among the ones imaged using the same scanner type and strength as the CAA group to minimize variability related to image acquisition, as described in a previous study from our group.[11] Age-matching among the 3 study cohorts was performed by matching each patient with CAA to a HC and a patient with AD based on the closest age to the first decimal, as previously described, before accessing and processing the MRIs, blinded to radiologic or other patient-specific characteristics.[11] Investigators performing the FreeSurfer-based automated imaging analyses were blinded to the diagnoses of individual participants.

In addition to MRI, demographics, vascular risk factors, and clinical, genetic, and neurocognitive data were also collected, as described in previous reports.[4,11] Part of the data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early AD.

Standard protocol approvals, registrations, and patient consents
This study was performed with the approval of and in accordance with the guidelines of the institutional review board of Massachusetts General Hospital. All participants provided written informed consent.

MRI acquisition
Structural MRI was performed on all patients with sporadic CAA using a Siemens (Munich, Germany) Avanto 1.5T scanner (with a 12-channel head coil). The standardized protocol included T1-weighted multiecho magnetization-prepared rapid gradient echo ($1 \times 1 \times 1$ mm^3 voxel size), high-resolution susceptibility-weighted imaging (SWI: $0.75 \times 0.75 \times 1.30$ mm^3 voxel size), and 3D fluid-attenuated inversion recovery (FLAIR) MRI ($1 \times 1 \times 1$ mm^3 voxel size) sequences.[11]

All participants obtained from the ADNI database underwent a similar structural MRI protocol, using Siemens 1.5T scanners. Further details on the MRI acquisition methods followed by ADNI have been described.[13]

Image processing

Three-dimensional cortical and subcortical reconstruction was performed using the FreeSurfer software suite (www.surfer.nmr.mgh.harvard.edu; version 5.3.0).[14–16] FreeSurfer is a fully automated suite of tools used for the analysis of neuroimaging data and has been used extensively in the literature in order to elucidate the structural and functional properties of the brain.[17]

The WMV of each hemisphere was calculated and defined as the total volume inside the gray–white junction minus the volume of nonwhite matter structures enclosed, such as the ventricles and subcortical gray matter structures.[18,19] All WMV measurements were inspected manually to ensure their accuracy, and manual interventions (via control points) were performed, when necessary, as described previously.[11] Manual processing was performed blinded to other imaging and clinical data.

Additional variables measured were cortical gray matter volume and estimated total intracranial volume (eTIV).[20] The latter allows for correction based on the variable head size of the individuals studied. To that end, all volumetric measures used in the current study were expressed as percent of eTIV, such as WMV percent of eTIV (pWMV). In order to assess the degree of CAA-related structural damage, the total number of lobar microbleeds was counted on high-resolution SWI MRIs, and white matter hyperintensity (WMH) volumes were calculated in 3D FLAIR MRIs using an in-house semiautomated algorithm.[11] All measurements are based on previously validated published guidelines, and all results were examined visually to verify their accuracy.[21,22]

Other volumes were also expressed as a percentage of eTIV (i.e., percent of intracranial gray matter volume [pGMV] and pWMH). In patients with intracerebral hemorrhage (ICH), the aforementioned variables were obtained from the nonaffected hemisphere and multiplied by 2 to calculate their volume as a percentage of eTIV.[11]

Neurocognitive evaluation

Based on formal testing, neurocognitive scores were calculated among patients with probable CAA without dementia.[9] From the total of 72 patients with CAA, 61 underwent a standard neurocognitive battery. The remaining 11 declined detailed neurocognitive evaluation. Baseline characteristics (age, sex, vascular risk factors, *APOE* status, number of microbleeds, and pWMV) did not differ between the patients who consented to undergo cognitive testing and the ones who declined ($p > 0.2$ for all comparisons). Verbal memory (immediate and delayed memory scores based on Hopkins Verbal Learning Test), processing speed (Trail-Making Test A, Symbol Substitution Test), and executive function (Trail-Making Test B, Digit Span Test backwards, verbal fluency test) were calculated as reported previously.[9] Each cognitive score was transformed into a *z* score by taking into account the mean and SD scores of the whole CAA cohort.[9]

Statistical analysis

Bivariate analyses were performed using χ^2 test for ratios and *t* tests for continuous variables. Data from all patients were entered in a general linear model (GLM) with pWMV as the dependent variable, group as a class variable, and other potential confounders as covariates. Tukey test was used to adjust for multiple comparisons among the 3 groups (CAA, AD, control). Age, sex, history of hypertension, microbleed counts, pGMV, pWMH volume, and presence of *APOE* ε4 allele were predefined variables of interest based on prior research; therefore, their associations with pWMV were tested, in addition to being used as covariates in GLM and other multiple regression models. *APOE* status was available for 68 of 72 patients with CAA and all participants in the HC and AD groups. Multiple regression models were performed both including and excluding the presence of *APOE* ε4 as a binary variable and the significant associations were unchanged. Results of models including *APOE* ε4 status are provided in the text. Presence of hyperlipidemia and diabetes did not correlate with the diagnostic categories, imaging, genetic, and cognitive markers of interest, so these 2 risk factors were not included in final regression analyses in order to avoid overfitting of the models. We checked the assumptions required for multiple regression models using scatterplots, residual analysis, and variance inflation factor values and these analyses showed linear relationship between the outcome variable and the independent variables, normal distribution of residuals, and no multicollinearity. The *z* scores of neurocognitive tests were calculated as described previously.[9] The statistical analyses were performed using IBM SPSS software version 24 (IBM Corporation, Armonk, NY) and JMP statistical software (version 14; SAS Institute Inc., Cary, NC). A threshold for significance of $p < 0.05$ was used. All tests of significance were 2-tailed.

A separate GLM was calculated using the voxel-based morphometry toolbox of the Statistical Parametric Mapping (version 12) software, in order to schematically explore the regional differences in WMV among patients with CAA, HC, and patients with AD, after adjusting for age, sex, and eTIV.[23] Regional topographic maps were generated using a threshold of $p < 0.001$; correction for multiple dependent comparisons was applied using the theory of Gaussian random fields.

Data availability

Any data not published within the article are available by request from a qualified investigator.

Results

The study population consisted of 72 patients with probable CAA without dementia, 72 age-matched HCs, and 72 age-matched patients with AD. Among the 72 patients with AD, 38 (52.8%) were in the early stages of the disease with a clinical dementia rating scale score of 0.5, and the remaining 34 had a clinical dementia rating scale of 1. Detailed characteristics for each cohort can be found in table 1.

Patients with CAA presented with significantly lower WMV expressed as a percentage of eTIV (pWMV) when compared to age-matched HCs and patients with AD ($p < 0.0001$ for both analyses; table 1). Those differences were most pronounced in the occipital lobes in both comparisons (figure). In order to remove the potential confounding effects of ICH presence, the same analyses were repeated in 32 ICH-free patients with CAA. This group again displayed less pWMV (28.13 [SD 2.57]) when compared with 32 age-matched HCs and 32 age-matched patients with AD ($p < 0.0001$ and $p = 0.004$, respectively; table 1).

Diagnosis of CAA was independently associated with lower pWMV in a GLM adjusting for age, sex, pGMV, pWMH volume, presence of *APOE* ε4, and presence of hypertension when compared to both HCs and patients with AD ($p < 0.0001$ for both associations, after correction for multiple comparisons; Tukey test). Within this model, higher age and presence of hypertension were significantly correlated with lower pWMV ($p = 0.004$ and $p = 0.027$, respectively). Presence of *APOE* ε4 was associated with lower pWMV ($p = 0.016$) whereas pWMH was not ($p = 0.923$). We then added an interaction term between hypertension and disease status to this GLM in order to look for the presence of a significant interaction between these important variables of interest. There was a significant interaction between disease status and presence of hypertension ($p = 0.03$) within this model. For this reason, we performed separate subgroup analyses within the groups of nonhypertensive and hypertensive patients with CAA and their matched controls to look for significant associations between CAA and pWMV. To that end, a subset of 32 nonhypertensive patients with CAA was compared to 32 nonhypertensive age-matched HCs and 32 nonhypertensive age-matched patients with AD. Similarly, a subset of 40 hypertensive patients with CAA was compared to 24 hypertensive age-matched HCs and 35 hypertensive age-matched patients with AD. The results remained unaltered in both cases; nonhypertensive and hypertensive patients with CAA had significantly lower pWMV (nonhypertensive CAA: 28.98 [SD 2.54]; hypertensive CAA: 27.16 [SD 2.45]) than their age-matched HCs and patients with AD (nonhypertensive cohorts: $p = 0.0003$ and $p = 0.013$, respectively; hypertensive cohorts: $p < 0.0001$ for both analyses; table 1).

Multiple regression models were performed on subsets of patients with CAA without ICH, as well as with and without hypertension, and their age-matched controls, in order to mitigate the confounding from potential widespread effects of these pathologies in CAA. Patients with CAA but no ICH again had significantly less pWMV than their age-matched HCs and patients with AD ($p = 0.011$ and $p = 0.003$, respectively). Similarly, hypertensive as well as nonhypertensive patients with CAA showcased significantly lower pWMV when compared to their matched HCs and patients with AD (hypertensive cohorts: $p = 0.0003$ and $p = 0.0004$, respectively; nonhypertensive cohorts: $p = 0.048$ and $p = 0.022$,

respectively). Overall, patients with CAA had significantly worse WMA than HCs and patients with AD when analyses were limited to both hypertensive and nonhypertensive cohorts but the differences were numerically more pronounced in the hypertensive CAA vs hypertensive AD/HC comparisons.

Within the CAA cohort, higher age and lobar microbleed counts were associated with lower pWMV ($p = 0.0007$ and $p = 0.031$, respectively; table 2). Hypertensive patients with CAA also had significantly lower pWMV than nonhypertensive patients with CAA ($p = 0.003$). The independent association between pWMV and lobar microbleed counts, within the CAA cohort, remained significant even after correcting for age, sex, hypertension, presence of *APOE* ε4, presence of ICH, pGMV, and pWMH volume ($p = 0.023$). In this model, higher age and presence of hypertension also correlated with lower pWMV ($p = 0.006$ and $p = 0.004$, respectively).

Among the 61 patients with CAA who had detailed neurocognitive evaluation, higher pWMV correlated with better scores of cognitive speed and executive function, but not with memory tests ($p = 0.024$, $p = 0.025$, and $p = 0.655$, respectively; table 2). Using the same multiple linear regression model as before, the independent correlation between higher pWMV and better scores of executive function persisted ($p = 0.037$), but no independent association was found between pWMV and processing speed or verbal memory scores ($p = 0.366$ and $p = 0.181$, respectively). Moreover, presence of *APOE* ε4 and increased pWMH volume correlated with worse executive function scores ($p = 0.038$ and $p = 0.003$, respectively).

Discussion

Our study demonstrates that patients with a diagnosis of CAA have lower white matter volumes when compared with either age-matched HCs or patients with AD. Our results indicate that vascular amyloid is likely to cause white matter atrophy (WMA) independent of the effects of age, hypertension, and parenchymal AD pathology. WMA correlated independently with the number of cortical microbleeds, a well-established marker of disease severity in CAA, further supporting a cause–effect relationship between vascular amyloid pathology and WMA. Finally, the association between severity of WMA and worse executive scores in patients with CAA suggests that WMA might be an independent mediator of cognitive worsening in CAA.

The observation that patients with CAA had greater WMA than patients with AD supports the interpretation that cerebrovascular amyloid rather than accompanying parenchymal amyloid plaques is the predominant driver of white matter injury. Age-matching is important to this interpretation, as age strongly correlates with brain atrophy. We also found a significant effect

Table 1 Comparisons among patients with cerebral amyloid angiopathy (CAA), healthy controls, and patients with Alzheimer disease (AD)

	Patients with CAA	Healthy controls	Mean difference vs CAA (95% CI; p value[a] or p value[b])	Patients with AD	Mean difference vs CAA (95% CI; p value[a] or p value[b])
All individuals					
No. of individuals	72	72	—	72	—
Age, y[a]	70.08 (7.91)	70.79 (2.54)	−0.71 (−1.97 to 0.55; 0.471)	70.08 (6.88)	0.00 (−0.23 to 0.24; 0.999)
Female[b]	16 (22.22)	33 (45.83)	0.003	32 (44.44)	0.005
Hypertension[b]	40 (55.56)	24 (33.33)	0.007	35 (48.61)	0.40
Hyperlipidemia[b]	30 (41.67)	40 (55.56)	0.096	41 (56.94)	0.067
Diabetes mellitus[b]	5 (6.94)	8 (11.11)	0.38	5 (6.94)	1.00
APOE ε4[b]	30 (44.12)	20 (27.78)	0.044	53 (73.61)	0.0004
White matter volume, % of eTIV[a]	27.97 (2.63)	30.35 (2.31)	−2.38 (−2.45 to −2.30; <0.0001)	29.54 (1.91)	−1.57 (−1.74 to −1.40; <0.0001)
Without intracerebral hemorrhage[c]					
No. of Individuals	32	32	—	32	—
Age, y[a]	70.92 (6.45)	70.92 (2.81)	0.00 (−1.32 to 1.31; 1.000)	70.92 (6.42)	0.00 (−0.02 to 0.00; 0.999)
White matter volume, % of eTIV[a]	28.13 (2.57)	30.95 (2.00)	−2.82 (−3.03 to −2.61; <0.0001)	29.73 (1.55)	−1.60 (−1.98 to −1.23; 0.004)
Without hypertension[d]					
No. of individuals	32	32	—	32	—
Age, y[a]	69.07 (7.36)	70.43 (3.33)	−1.36 (−2.82 to 0.09; 0.344)	69.38 (6.58)	−0.31 (−0.60 to −0.03; 0.857)
White matter volume, % of eTIV[a]	28.98 (2.54)	31.09 (1.71)	−2.11 (−2.40 to −1.81; 0.0003)	30.33 (1.51)	−1.35 (−1.72 to −0.97; 0.013)
With hypertension[e]					
No. of individuals	40	24	—	35	—
Age, y[a]	70.90 (8.32)	70.80 (1.92)	0.10 (−1.75 to 1.95; 0.944)	70.33 (6.84)	0.57 (0.26–0.88; 0.747)
White matter volume, % of eTIV[a]	27.16 (2.45)	30.55 (2.29)	−3.39 (−3.57 to −3.2; <0.0001)	29.24 (1.90)	−2.08 (−2.21 to −1.95; <0.0001)

Abbreviations: CI = confidence interval; eTIV = estimated total intracranial volume.
APOE status was available in 68 patients with CAA and all participants in comparator groups. Values are mean (SD) or n (%) unless otherwise indicated.
[a,b]Statistical difference vs CAA was expressed as [a]mean difference vs CAA (95% CI; p value) for continuous variables (i.e., age and white matter volume) and as [b]χ^2 statistic p value for discrete variables (i.e., sex, hypertension, hyperlipidemia, diabetes mellitus, and *APOE* ε4). Healthy controls and patients with AD were age-matched to patients with CAA.
[c] Analysis after inclusion of patients with CAA who did not present with intracerebral hemorrhage compared to age-matched healthy controls and patients with AD.
[d] Analysis after inclusion of nonhypertensive patients with CAA compared to nonhypertensive age-matched healthy controls and patients with AD.
[e] Analysis after inclusion of hypertensive patients with CAA compared to hypertensive age-matched healthy controls and patients with AD.

Figure Regional white matter volume differences between a cohort of patients without dementia with probable cerebral amyloid angiopathy (CAA) and 2 other age-matched cohorts: a cohort of patients with Alzheimer disease (AD) and a healthy control cohort
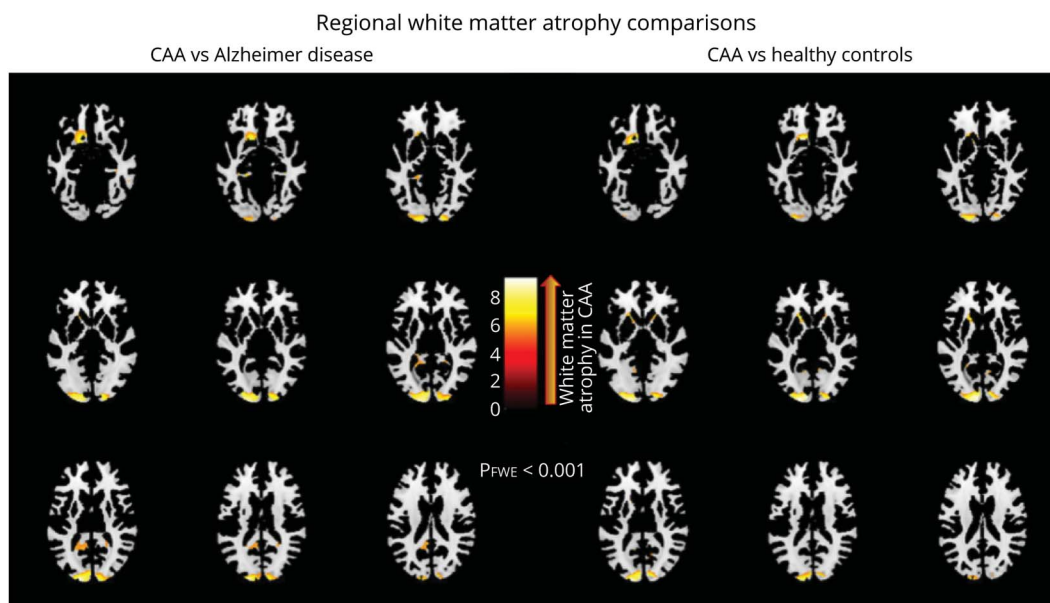
Voxel-based morphometry through statistical parametric mapping 12 software was used to explore the regions where white matter volume (adjusted for age, sex, and total intracranial volume) was significantly lower in patients without dementia with probable CAA when compared to age-matched healthy controls and patients with AD (lighter colors correspond to regions of worse white matter atrophy in CAA). A general linear model was performed, and regional surface maps were generated using a threshold of $p < 0.001$ (with additional correction for multiple comparisons).

of hypertension on WMA in CAA, but the association between CAA and WMA appeared independent of hypertension based on 3 analytic approaches: (1) the 32 patients with CAA without hypertension had lower pWMV compared to age-matched nonhypertensive HCs and patients with AD; (2) the 40 patients with CAA with hypertension had lower pWMV compared to age-matched hypertensive HCs and patients with AD and these differences appeared to be numerically more significant than differences found in nonhypertensive participants; (3) the association between CAA and WMA was independent of hypertension in multiple regression models. Another potential confounder is prior ICH, which might trigger WMA by perihematomal effects or remote Wallerian degeneration. In addition to using volumetric measures from the hemisphere without ICH in all comparisons, we repeated analyses in patients without ICH, once again finding similar results. Taken together, our results indicate that CAA-related WMA is independent of age, sex, AD pathology, hypertension, ICH, and *APOE* ε4 status but hypertension and CAA might potentiate each other's effect on WMA. The latter finding, based on a post hoc analysis in our study, will need to be confirmed in larger studies as it also gives rise to intriguing questions about the mechanisms of interactions between hypertension and CAA. Potential hypotheses might include increased accumulation of vascular amyloid in the presence of hypertension or other mechanisms that might involve interactions of CAA and hypertension specifically potentiating the pathologic pathways that lead to white matter damage.

Lobar CMBs are tiny hemorrhagic lesions and well-established markers of CAA diagnosis and disease severity.[21,24,25] The observed association between higher lobar microbleed counts and lower pWMV further supports the causative role of CAA in WMA, suggesting a dose–response relationship with CAA disease severity. Our data also suggest an impact of CAA-related WMA on brain function, demonstrating a correlation with executive function and processing speed. CAA has been established as an independent contributor to dementia in the general population and in patients diagnosed with CAA during life.[6,7,26] The cognitive domains preferentially affected in CAA are executive function and processing speed, i.e., domains typically associated with subcortical tissue injury.[27] Episodic memory is less clearly affected in CAA and was not associated with WMA in the current analysis.[7,9] An important question to be addressed in larger data sets is which of the various markers of subcortical brain injury in CAA (such as WMH and altered diffusion tensor imaging properties along with the currently demonstrated WMA) identifies the predominant type of white matter injury most responsible for CAA-related cognitive dysfunction.

The physiologic mechanism for white matter injury in CAA has not been fully established but is likely mediated by vascular dysfunction and ischemia. CAA has been linked to alterations in vascular physiology such as impaired reactivity to physiologic stimulation and to other markers of white matter injury such as WMH and altered diffusion tensor

Table 2 Bivariate associations between white matter volume, expressed as % of estimated total intracranial white matter volume (pWMV), and pertinent variables in patients with cerebral amyloid angiopathy (CAA)

	Patients with CAA (n = 72)
Bivariate correlations of pWMV with continuous variables	
Age[a]	−0.391; 0.0007
Gray matter volume, % of eTIV[a]	0.192; 0.107
White matter hyperintensity volume, % of eTIV[a]	−0.084; 0.484
Lobar microbleeds[a]	−0.257; 0.031
Verbal memory *z* score[a] (n = 61)	0.060; 0.655
Processing speed *z* score[a] (n = 61)	0.288; 0.024
Executive function *z* score[a] (n = 61)	0.286; 0.025
Comparison of mean pWMV within binary variables	
Sex (female vs male)[b]	−0.18 (−1.17 to 0.81; 0.836)
Hypertension (presence vs absence)[b]	−1.82 (−1.96 to −1.69; 0.003)
Hyperlipidemia (presence vs absence)[b]	0.45 (0.21–0.69; 0.485)
Diabetes mellitus (presence vs absence)[b]	−1.02 (−1.70 to −0.34; 0.115)
***APOE* ε4 (presence vs absence)**[b] (n = 68)	−0.50 (−0.63 to −0.37; 0.437)
Intracerebral hemorrhage (presence vs absence)	−0.29 (−0.35 to −0.22; 0.647)

Abbreviation: eTIV = estimated total intracranial volume.
[a] Association reported as correlation coefficient; *p* value.
[b] Association reported as mean difference (95% confidence interval; *p* value).

imaging properties.[9,28,29] We note that WMA in the current study has a predilection for posterior white matter (figure), reminiscent of previous studies showing posterior predominance of microbleeds, WMH, and vascular amyloid itself.[30–32] It might be hypothesized that more severe posterior vascular amyloid load consistently seen in CAA is causing more severe vascular dysfunction and resultant WMA in these posterior regions. In this context, the lack of a strong association between WMA and WMH volume is a notable and somewhat unexpected finding. This may simply reflect the modest sample size, but also raises the possibility that different mechanisms are responsible for these 2 types of injury. WMH is thought to represent tissue rarefaction whereas brain atrophy represents bona fide tissue loss. Although chronic CAA-related ischemia would be hypothesized to be the main cause of both WMA and WMH, there might be different mediators including preferential effects of CAA-related small lesions such as microbleeds or microinfarcts on WMA. This report is a first step establishing WMA as a consequence of CAA and a potential marker of

disease severity, but it will require additional analyses (likely using larger cohorts) to elucidate the underlying mechanisms.

Our study has some limitations. The sample size is large relative to previous in-depth MRI-based studies of CAA, but nonetheless modest enough to limit the statistical power of subgroup analyses. CAA in these participants is diagnosed by pattern of hemorrhages rather than by neuropathology, but previous radiologic–pathologic validation analyses have demonstrated the Boston Criteria to have high specificity.[12] Residual confounding of the results by accompanying processes such as AD cannot be excluded and were addressed in the current analysis by direct comparison to an age-matched AD group imaged with the same scanner type and field strength. All patients with CAA were scanned in the same Siemens 1.5T scanner whereas HCs and patients with AD were scanned in Siemens 1.5T scanners at different centers. Even though scanners of the same brand and same field strength were used for this study, it would be ideal to reproduce the reported findings in future studies by enrolling patients with CAA and comparator groups at multiple sites using the exact same set of scanners. Furthermore, the multiple regression models used address the linear relationships between WMV and other variables of interest. However, it might be of value to also explore in future studies any potential nonlinear effects between the same variables, using larger cohorts. Finally, even though accessibility of imaging processing software in the clinical setting is an ongoing process, we hope that this study can serve as a stepping stone for the wider clinical utility of imaging markers such as WMA.

Overall, posterior-predominant WMA appears to be significantly more pronounced in CAA compared to HCs and AD. WMA in CAA also independently correlates with markers of CAA disease severity (CMB counts) and scores of executive function. WMA might thus represent an important mediator of the neurologic dysfunction related to CAA and a potential marker for future observational studies or a target for interventional trials of this largely untreatable disease.

Study funding

Disclosures

Publication history

Appendix Authors

Name	Location	Contribution
Panagiotis Fotiadis, BSc	Hemorrhagic Stroke Research Program, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston	Literature search, figures, study design, data collection, imaging data analysis, statistical analysis, data interpretation, manuscript writing
Yael D. Reijmer, PhD	Hemorrhagic Stroke Research Program, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston	Literature search, imaging data analysis, critical review of the manuscript
Susanne J. Van Veluw, PhD	Hemorrhagic Stroke Research Program, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston	literature search, imaging data analysis, critical review of the manuscript
Sergi Martinez-Ramirez, MD	Hemorrhagic Stroke Research Program, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston	Imaging data analysis, critical review of the manuscript

Appendix *(continued)*

Name	Location	Contribution
Fikret Isik Karahanoglu, PhD	Hemorrhagic Stroke Research Program, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston	Literature search, imaging data analysis, critical review of the manuscript
Elif Gokcal, MD	Hemorrhagic Stroke Research Program, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston	Literature search, imaging data analysis, critical review of the manuscript
Kristin M. Schwab, BA	Hemorrhagic Stroke Research Program, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston	Data collection, critical review of the manuscript
Joshua N. Goldstein, MD, PhD	Division of Neurocritical Care and Emergency Neurology, Massachusetts General Hospital, Harvard Medical School, Boston	Data collection, critical review of the manuscript
Jonathan Rosand, MD, MSc	Division of Neurocritical Care and Emergency Neurology, Massachusetts General Hospital, Harvard Medical School, Boston	Data collection, critical review of the manuscript
Anand Viswanathan, MD, PhD	Hemorrhagic Stroke Research Program, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston	Data collection, critical review of the manuscript
Steven M. Greenberg, MD, PhD	Hemorrhagic Stroke Research Program, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston	Data collection, data interpretation, manuscript writing
M. Edip Gurol, MD, MSc	Hemorrhagic Stroke Research Program, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston	Literature search, figures, study design, data collection, imaging data analysis, statistical analysis, data interpretation, manuscript writing

Appendix 2 Coinvestigators

A complete listing of ADNI investigators can be found in the coinvestigators list at links.lww.com/WNL/B135.

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