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AJNR Am J Neuroradiol published online 8 June 2023
http://www.ajnr.org/content/early/2023/06/08/ajnr.A7900

Published June 8, 2023 as 10.3174/ajnr.A7900

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ABSTRACT

BACKGROUND AND PURPOSE: Cerebral amyloid angiopathy is characterized by amyloid β deposition in leptomeningeal and superficial cortical vessels. Cognitive impairment is common and may occur independent of concomitant Alzheimer disease neuropathology. It is still unknown which neuroimaging findings are associated with dementia in cerebral amyloid angiopathy and whether they are modulated by sex. This study compared MR imaging markers in patients with cerebral amyloid angiopathy with dementia or mild cognitive impairment or who are cognitively unimpaired and explored sex-specific differences.

MATERIALS AND METHODS: We studied 58 patients with cerebral amyloid angiopathy selected from the cerebrovascular and memory outpatient clinics. Clinical characteristics were collected from clinical records. Cerebral amyloid angiopathy was diagnosed on MR imaging on the basis of the Boston criteria. Visual rating scores for atrophy and other imaging features were independently assessed by 2 senior neuroradiologists.

RESULTS: Medial temporal lobe atrophy was higher for those with cerebral amyloid angiopathy with dementia versus those cognitively unimpaired ($P = .015$), but not for those with mild cognitive impairment. This effect was mainly driven by higher atrophy in men with dementia, compared with women with and without dementia ($P = .034$, $P = .012$; respectively) and with men without dementia ($P = .012$). Enlarged perivascular spaces in the centrum semiovale were more frequent in women with dementia versus men with and without dementia ($P = .021$, $P = .011$; respectively) and women without dementia ($P = .011$).

CONCLUSIONS: Medial temporal lobe atrophy was more prominent in men with dementia, whereas women showed a higher number of enlarged perivascular spaces in the centrum semiovale. Overall, this finding suggests differential pathophysiologic mechanisms with sex-specific neuroimaging patterns in cerebral amyloid angiopathy.

ABBREVIATIONS: Aβ = amyloid β; AD = Alzheimer disease; ARWMC = age-related white matter changes; CAA = cerebral amyloid angiopathy; cSS = cortical superficial siderosis; EPVS = enlarged perivascular spaces; IQR = interquartile range; MCI = mild cognitive impairment; MTA = medial temporal lobe atrophy

Cerebral amyloid angiopathy (CAA) is pathologically characterized by amyloid β (Aβ) deposition in the walls of leptomeningeal and cortical small vessels.[1] Clinically, it is a major cause of intracerebral hemorrhage, and it may present not only as other acute neurologic manifestations, such as transient focal neurologic episodes, but also with slowly progressive cognitive impairment.[2] In vivo diagnosis has been made possible by the Boston diagnostic criteria, which require the presence of multiple lobar microbleeds, multiple major lobar hemorrhages, and a single hemorrhage accompanied by cortical superficial siderosis (cSS), with other causes having been excluded.[2] The recently proposed version 2 of the Boston criteria for diagnosis of CAA additionally included the presence of nonhemorrhagic markers such as a high burden of enlarged perivascular spaces (EPVS) in the centrum semiovale and a multispot pattern of white matter hyperintensities.[3]

Received January 23, 2023; accepted after revision May 7.

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The research of A.S. Costa is supported by a START Grant (118/20) from the Faculty of Medicine of the RWTH Aachen University. No other specific allocated funding is reported.

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Indicates article with online supplemental data.

http://dx.doi.org/10.3174/ajnr.A7900

Structural MR imaging studies in CAA demonstrate an intermediate pattern of atrophy between cognitively healthy and the one seen in Alzheimer's disease (AD).[4,5] Additionally, AD is frequently associated with CAA, with more than 80% of patients with AD on postmortem examination showing at least some degree of CAA pathology.[6] Furthermore, studies evaluating the effect of CAA on cognition have suggested that it might play an independent role in cognitive impairment, potentially with a pattern of cognitive deficits distinct from that found in typical AD,[7-11] even though this connection is still under study.[12] However, the relationship between cognitive impairment in patients with CAA and brain atrophy has not been studied in detail. Moreover, while sex-specific differences have been found in AD, few studies have explored their effect in CAA.[13]

Another imaging marker of increasing interest in CAA is the observation of EPVS visible on MR imaging. EPVS in the centrum semiovale have been associated with increased cortical vascular Aβ in the overlying cortex[14,15] and indirect measures of CAA severity, such as cortical microbleeds and cSS.[16-18] Altogether, these findings suggest that impaired perivascular drainage of Aβ might be associated with a higher frequency of EPVS in the centrum semiovale. However, whether these imaging findings are associated with cognitive impairment in CAA and whether they might be differentially modulated by sex have not been studied.

Our goal was to study brain MR imaging features in CAA, such as cerebral atrophy and the frequency of EPVS, and their relationship with the severity of cognitive impairment and sex in patients with CAA.

MATERIALS AND METHODS

Statement of Ethics

The study was approved by the Ethics for Health Commission of Hospital de Braga.

Patient Clinical and Imaging Data

This was a retrospective study of adult patients with possible or probable CAA according to the modified Boston criteria,[3] diagnosed in the Department of Neurology of Hospital de Braga during a 4-year period. Patients with a diagnosis of CAA were selected after an analysis of all individual records of patients attending the cerebrovascular outpatient clinic and the memory outpatient clinic during the study period. All patients underwent 1.5T brain MR imaging (including T1-, T2-, and T2*-weighted images and T2 FLAIR). MR imaging acquisition protocol was constant throughout the study period. Demographic and clinical variables were collected from the digital clinical records. Patients were followed in the neurology outpatient clinic as part of the routine clinical care. Diagnosis of mild cognitive impairment (MCI) and dementia according to local and international guidelines[19,20] was based on clinical evaluation and available clinical records from the neurology outpatient clinic. MCI was defined as the presence of cognitive symptoms expressed by the patient or next-of-kin, with objective impairment in at least 1 domain of cognitive function and absence of impairment on social or occupational functioning.[19] Dementia was defined as the presence of cognitive impairment severe enough to interfere with the activities of daily living.

Imaging Score Assessments

MR images were independently reviewed by 2 experienced neuroradiologists, blinded to clinical information, for the classification of the following: the presence of cSS (focal = restricted to 3 sulci, disseminated = involving >3 sulci) on axial T2* acquisitions; age-related white matter changes (ARWMC) using axial T2 FLAIR acquisitions at the level of basal ganglia (0 = no lesions; 1 = 1 focal lesion [≥5 mm]; 2 ≥ 1 focal lesion; 3 = confluent lesions) and centrum semiovale (0 = no lesions; 1 = focal lesions; 2 = beginning confluence of lesions; 3 = diffuse involvement of the entire region with or without U-fiber involvement);[21] and the semiquantitative scale measuring the burden of EPVS using axial T2 acquisitions in the basal ganglia and centrum semiovale (0 = none; 1 = 1–10; 2 = 11–20; 3 = 21–40; 4 ≥ 40).[22] Brain regional atrophy was assessed using a group of validated MR imaging visual rating scales on the following regions: anterior cingulate (graded from 0 to 3), orbitofrontal (graded from 0 to 3), anterior temporal (graded from 0 to 4), frontoinsular (graded from 0 to 3), medial temporal (graded from 0 to 4), and posterior regions (graded from 0 to 3).[23] For each brain region scale, the average of both hemispheres was calculated, and an average of both classifiers was used. Brain regions affected by intracerebral hemorrhage or encephalomalacia from a previous hemorrhage were excluded from assessment. Relative levels were computed as a percentage of maximum possible atrophy for each regional scale. Reference images for each rating scale were provided to the classifiers on the basis of Harper et al,[23] to aid the rating process. Interobserver agreement was calculated using the intraclass correlation coefficient for single measures with the 95% CI (Online Supplemental Data). Disagreements of >1 in each rating score were reviewed by the 2 raters, and a consensus was reached.

Statistical Analysis

Demographic and clinical characteristics of patients with CAA with normal cognition, MCI, and dementia were compared using a 1-way ANOVA with a Tukey honestly significant difference correction for multiple comparisons, the χ^2 test, and the Fisher exact test, as appropriate. Visual rating scores were compared among cognition status groups using pair-wise Wilcoxon tests with Bonferroni correction for multiple comparisons. For analyses based on dementia status, patients with normal cognition and MCI were merged to constitute a group without dementia, and patients with dementia remained as the dementia group. Demographic and clinical comparisons were performed using a Welch *t* test or Wilcoxon tests, as appropriate. Regional brain atrophy scores were compared between sex and dementia groups using pair-wise Wilcoxon tests with a Bonferroni correction for multiple comparisons. ARWMC in the basal ganglia and centrum semiovale correlations with regional brain volumes were performed using the Spearman correlation. Regional brain volumes in the group positive for cSS were compared with those in the group negative for cSS using the Wilcoxon test. For the multivariable linear regression using medial temporal lobe atrophy (MTA) as the dependent variable, age was coded as a continuous variable, and sex and the presence of cSS and dementia, as categoric variables, constituting the independent variables, with a dementia × sex interaction. Contrast testing was then performed for group-of-interest comparison, and *P* values were corrected with the Bonferroni method for multiple comparisons. For comparison

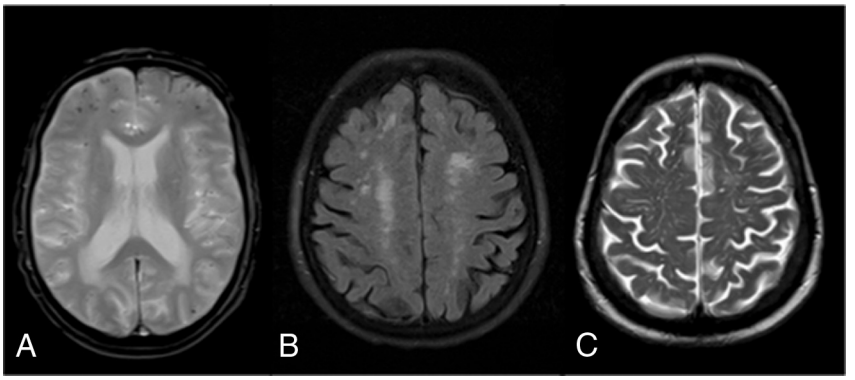

FIG 1. Brain MR imaging pathologic features of CAA pathology. *A*, Axial T2* image from a 76-year-old male patient shows left frontal cortical siderosis and multiple foci of microhemorrhages of the predominant frontal location bilaterally. *B*, Axial T2 FLAIR image from a 73-year-old woman shows centrum semiovale white matter T2-hyperintense lesions attributed to chronic small-vessel ischemia. *C*, Axial T2 image from a 78-year-old female patient shows EPVS in the centrum semiovale.

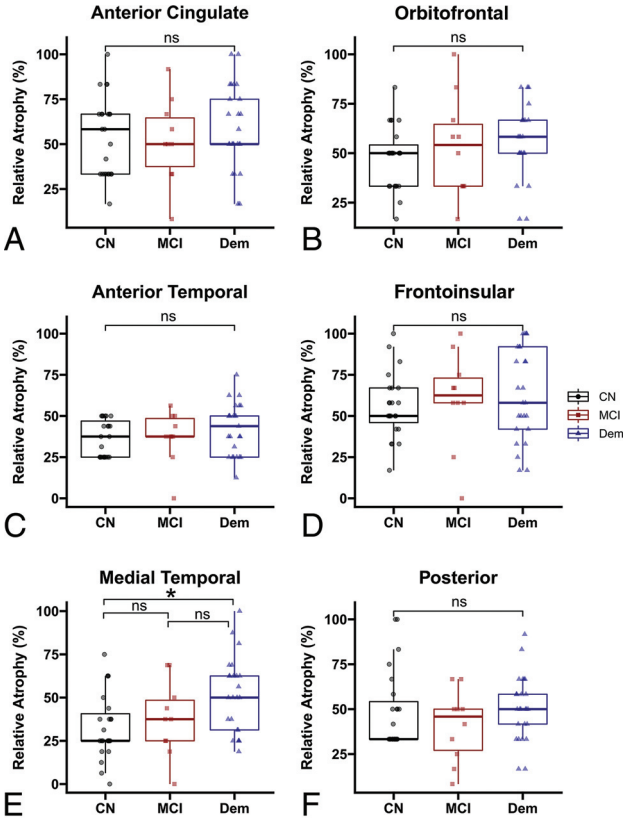

FIG 2. Regional brain atrophy as measured by the visual rating score compared across cognition levels: normal, MCI, dementia. The regions evaluated are the anterior cingulate (*A*), orbitofrontal (*B*), anterior temporal (*C*), frontoinsular (*D*), medial temporal (*E*), and posterior (*F*) . Statistical significance is considered at *P* values < .05 (*asterisk*). CN indicates cognitively unimpaired; Dem, dementia; ns, not significant.

of scores of EPVS among groups, we used pair-wise Wilcoxon tests with a Bonferroni correction for multiple comparisons. All statistical analyses were conducted using RStudio, Version 1.4.1103 (http://rstudio.org/download/desktop).

RESULTS

Our study population consisted of 58 patients, with a mean age of 71.6 (SD, 9.8) years, and 50% were men. Most of the patients were selected from the cerebrovascular outpatient clinic (n = 48, 83%), and the remainder were selected from the memory clinic (n = 10, 17%). All cases were confirmed to show characteristic CAA findings on brain MR imaging (Fig 1). Most patients presented with vascular risk factors: Hypertension was present in 78%; dyslipidemia, in 59%; and diabetes mellitus, in 22% of patients. Among our study population, 23 patients (40%) presented with normal cognition, 10 presented with MCI (17%), and 25 presented with dementia (43%). Baseline characteristics of the study population according to the presence of normal cognition, MCI, or dementia are presented in the Online Supplemental Data. The group with dementia was older than the group with normal cognition (P = .004).

Regarding visual rating scores for each brain region, increased MTA was found in patients with dementia compared with patients with normal cognition (P = .015; normal cognition: median = 25; interquartile range [IQR] = 15.65; dementia: median = 50; IQR = 31.2; Fig 2). There were no significant pair-wise differences across groups in the other brain regions.

Mediators of MTA

We analyzed the relationship between MTA and other variables such as sex, age, the presence of cSS, and the Fazekas score. Characteristics of patients with and without dementia and by sex are shown in the Online Supplemental Data.

We found more severe MTA in male patients with dementia compared with female patients with dementia (P = .034; female dementia: median = 50.0; IQR = 34.4; male dementia: median = 62.5; IQR = 25.1) and compared with men without dementia (P = .012; men with no dementia: median = 31.3; IQR = 21.9) and women without dementia (P = .012; women with no dementia: median = 31.3; IQR = 12.5; Fig 3). There were no significant differences in other brain regions. More severe MTA was observed in patients with cSS (P = .017; cSS: median = 46.9; IQR = 35.9; no cSS: median = 25.0; IQR = 21.8; Fig 4*A*). We also observed more severe atrophy of the posterior and anterior cingulate regions in patients with cSS (Online Supplemental Data). More severe MTA was also associated with increased white matter hyperintense lesions in both the basal ganglia (ρ = 0.59, P < .001) and the periventricular white matter (ρ = 0.47,

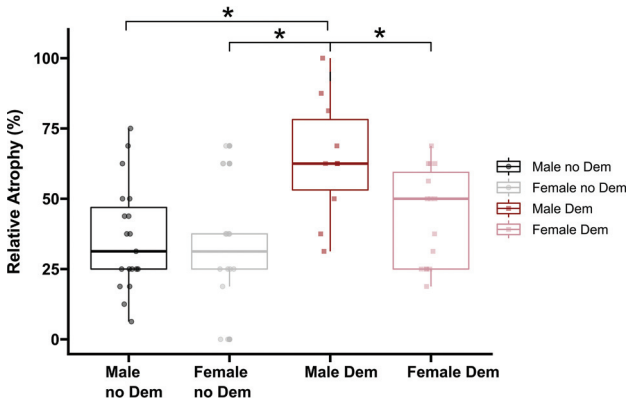

FIG 3. MTA as measured by the visual rating scale across dementia groups and sex: Male no Dem; Female no Dem; Male Dem; Female Dem. Statistical significance is considered at *P* values < .05. Dem indicates dementia.

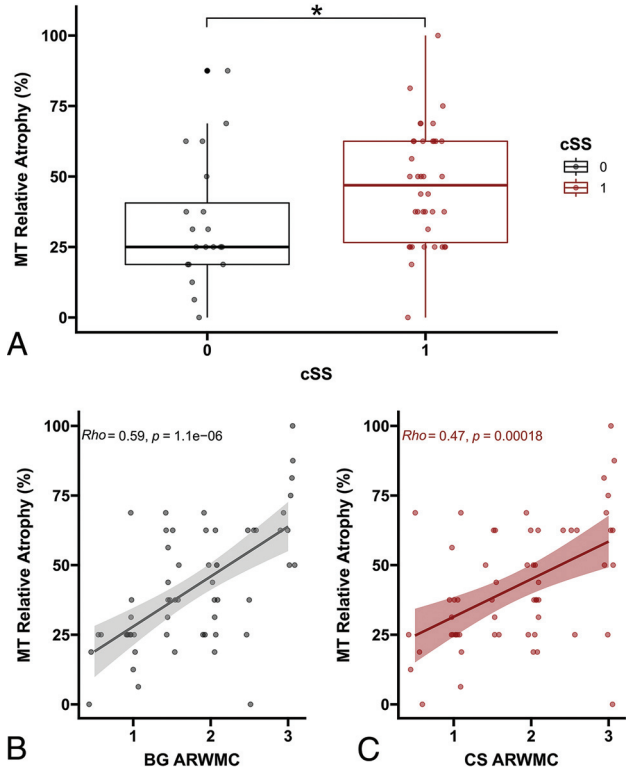

FIG 4. Determinants of MTA in CAA. *A*, MTA as measured by visual rating across the presence (1) or absence (0) of cSS. *B*, Spearman correlation analysis of MTA with basal ganglia age-related white matter changes (BG ARWMC). *C*, Spearman correlation analysis of MTA with centrum semiovale age-related white matter changes (CS ARWMC). Statistical significance is considered at *P* values < .05 (*asterisk*). MT indicates medial temporal lobe.

P < .001; Fig 4*B*, -*C*). We found this same pattern of association for all brain regions (Online Supplemental Data).

To confirm the sex-specific results, we conducted a multivariable linear regression model with age, sex, and the presence of cSS and dementia as independent variables, including a dementia × sex interaction, and MTA as the dependent variable (Online Supplemental Data). Increasing age was associated with increased MTA (*P* < .010), and contrast tests (Online Supplemental Data) revealed that male patients with dementia have significantly greater atrophy compared with female patients with dementia (*P* = .025) and compared with male patients without dementia (*P* = .011).

Frequency of EPVS

We assessed whether the frequency of EPVS was different according to the cognitive status of the patient. We found that the burden of EPVS is increased in the centrum semiovale but not in the basal ganglia in patients with dementia versus those with normal cognition (*P* = .023; normal cognition: median = 2.0; IQR = 1.75; dementia: median = 3.0; IQR = 1.5; Fig 5*A*, -*B*). When we divided the groups according to sex and the presence of dementia, we found that women with dementia showed a higher burden of EPVS in the centrum semiovale compared with men with dementia (*P* = .021; female dementia: median = 3.5; IQR = 1.0; male dementia: median = 2.0; IQR = 1.4) and with women without dementia (*P* = .011; women without dementia: median = 1.25; IQR = 1.5) and men without dementia (*P* = .011; men without dementia: median = 2.5; IQR = 2.0; Fig 5*C*).

DISCUSSION

Our results indicate a sex-specific pattern of cerebral atrophy and EPVS in patients with CAA and dementia. More severe MTA was associated with dementia in male patients with CAA but not in women, whereas a higher frequency of EPVS in the centrum semiovale was associated with dementia in female patients but not in male patients.

AD and CAA are frequently associated and share common pathophysiological pathways.[1,24] Accordingly, decreased hippocampal volume, a known feature of AD, is also found to a lesser degree in sporadic CAA,[5] and MTA has been implicated as a predictor of incidental dementia in patients with CAA.[25] We found that the medial temporal lobe is the only brain region evaluated in our study to be correlated with dementia (Fig 2), in line with these previous observations.

Sex-specific differences have also been reported, with increased severity of CAA pathology found in male patients with AD, independent of age and AD neuropathologic severity.[13] Our results indicate that male patients with dementia have more severe MTA than women with dementia, even after correction for major confounders such as age and the presence of cSS (Fig 3 and Online

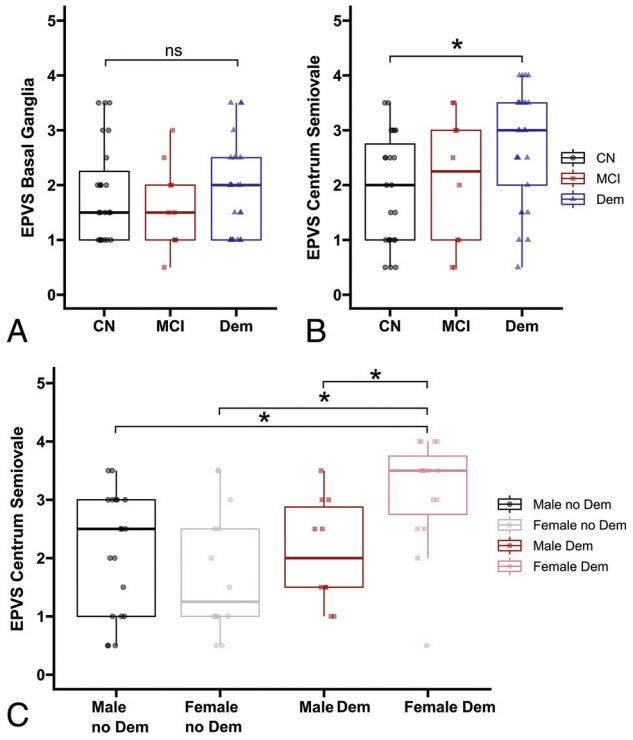

FIG 5. EPVS across cognition groups. *A*, Basal ganglia EPVS. *B*, Centrum semiovale EPVS. *C*, Centrum semiovale EPVS across dementia by sex groups. Statistical significance is considered at *P* values < .05 (*asterisk*). CN indicates cognitively unimpaired; Dem, dementia; ns, not significant.

Supplemental Data), suggesting that, in CAA, sex might play a differential role in neurodegeneration in this brain region.

The mechanisms underlying brain atrophy in patients with CAA are not fully understood. It is thought, however, that the consequences of the amyloidotic small-vessel disease, such as cortical microinfarcts, white matter lesions, and ischemic demyelination are important contributors to cortical thinning in CAA.[24] Concomitant AD pathology is likely an additional contributor to brain atrophy in some patients with CAA, but how often and to what extent remain unclear.[1] Most interesting, the increased severity of CAA in male patients with AD has been interpreted as a sign of higher susceptibility to vascular damage.[13] Accordingly, this sex-related small-vessel disease susceptibility might explain why men with dementia have higher atrophy than women with dementia, whereas the putative contribution from parenchymal amyloid might add to increased atrophy relative to men without dementia. Recently, men with sporadic CAA were shown to present with an earlier onset of disease and a more hemorrhagic phenotype compared with women, supporting the hypothesis of increased vascular burden in these patients.[26] The fact that dementia in women was not significantly associated with more severe MTA compared with women without dementia might suggest that, at least partially, different factors in the pathophysiology of the disease may play a role.

We have found that the burden of EPVS in the centrum semiovale but not in the basal ganglia is higher in patients with dementia (Fig 5). This is in line with the general dichotomy of basal ganglia EPVS being associated with small-vessel disease arteriolosclerosis, and the centrum semiovale EPVS with CAA.[27] Remarkably, we found a higher burden of EPVS in the centrum semiovale in female patients with dementia (Fig 5), suggesting a possible dementia mechanism in this sex group. Indeed, the presence of these enlarged spaces has been associated with vascular Aβ deposition,[14,15] which is in accordance with the hypothesis that centrum semiovale EPVS are associated with impaired perivascular drainage of Aβ. Our results provide further evidence in support of this hypothesis. However, centrum semiovale EPVS in AD are associated with cognitive impairment independent of amyloid burden.[28] The mechanisms behind this association thus remain to be established. Furthermore, sex differences in the burden of perivascular spaces have not been found in other CAA cohorts,[26,29] but these studies have not examined the joint effect of sex and dementia. Future work is needed to assess the mediation of sex and cognitive status on the prevalence of neuroimaging findings in CAA.

Even though our results support previous observations from the literature, there are relevant limitations in this study that should be considered. The small sample size limits generalization and the possibility of controlling for other confounders. Absent systematic detailed neuropsychological data for our cohort are also a relevant limitation, which precludes further analyses related to the clinical significance of regional atrophy or atrophy patterns. Additionally, the lack of neuropathologic data does not allow the verification of the etiology of dementia and the opportunity to assess the contribution of parenchymal and vascular pathology to cerebral atrophy. Despite these limitations, our findings are aligned with previous literature and suggest sex-differential mechanisms of dementia in patients with CAA. Future studies should address neuropathologically confirmed cases or alternatively use biologic biomarkers such as blood or CSF markers or PET data.

Finally, we used structured semiquantitative visual assessments for each of the neuroimaging metrics, which have less spatial and numeric granularity than automated quantitative techniques. While the latter are in the process of entering clinical practice, visual semiquantitative scores are easy to implement and ready to use by neuroradiologists. Visual rating scores for atrophy assessment have been consistently shown to correlate with automated volume quantification across different studies.[23,30-32] This finding suggests that, overall, visual rating scales have regional specificity and are sensitive to volume variations, even though at a lower resolution and detail. Future studies using regional volume quantification are needed to study atrophy patterns in patients with CAA and dementia and their modulation by sex. While still in development, new techniques of perivascular space segmentation have opened

up the possibility of including numerous metrics, encompassing volume, dimensions, and shape, to study their function.[33] Given the importance of this marker in CAA, future work contemplating these approaches may reveal new insights into the role of perivascular spaces. Regarding microbleeds, new methods are currently in development,[34] and regarding white matter hyperintensities, there is now a variety of segmentation packages available for use.[35,36] Future work implementing quantitative techniques is needed to confirm these results and potentially explore new associations with more detailed analysis of these neuroimaging findings.

CONCLUSIONS

Dementia in CAA appears to be associated with more marked MTA in men, whereas in women, a higher burden of EPVS in the centrum semiovale was observed. Overall, this finding suggests that there may be differential pathophysiologic mechanisms with sex-specific neuroimaging patterns in dementia in CAA, motivating further confirmatory studies in larger, independent cohorts.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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