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Early-Stage MRI Volumetric Differences in White Matter Hyperintensity and Temporal Lobe Volumes between Autopsy-Confirmed Alzheimer's Disease, Cerebral Small Vessel Disease, and Mixed Pathologies

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Keywords
Volumetry · Alzheimer's disease · Cerebral small vessel disease · Mild cognitive impairment

Abstract
Introduction: Alzheimer's disease (AD) and cerebral small vessel disease (CVSD) both contribute to age-related cognitive decline but can be difficult to clinically distinguish at early stages. At mild cognitive impairment (MCI), we investigated brain MRI volumetric differences in white matter hyperintensities (WMH), frontal and temporal lobe volumes between neuropathologically defined groups of cerebral arteriolosclerosis alone (pARTE), AD alone (pAD), and mixed (ADARTE). ***Methods:*** From the National Alzheimer's Coordinating Center, we defined neuropathology groups of pARTE (n = 18), pAD (n = 36), and ADARTE (n = 55) who had MRI brain volumetrics within 1 year of clinical evaluation with Clinical Dementia Rating score of 0.5, corresponding to MCI. We included moderate-to-severe arteriolosclerosis and/or ABC score 2–3 for AD, after excluding other major neuropathologies. We compared WMH and frontal and temporal lobe volumes between neuropathology groups using regression analysis. ***Results:*** Adjusted regression models show AD-related groups associated with less WMH when compared to pARTE (pAD adjusted odds ratio (aOR) (95% confidence interval [CI]): 0.94 (0.90–0.98); ADARTE aOR (95% CI): 0.96 (0.93–0.99)). The mixed pathology group, but not pAD, had smaller right temporal lobe volumes than pARTE (pAD aOR [95% CI]: 0.86 [0.74–1.00]; ADARTE aOR [95% CI]: 0.83 [0.72–0.96]). There were no differences in frontal lobe volumes. ***Discussion/Conclusions:*** Findings from this neuropathologically confirmed cohort suggest volumetric differences in WMH and temporal lobe volumes between AD- and CVSD-related MCI. Moreover, our results suggest a differential atrophy susceptibility of the right versus left temporal lobe to the additive effect of AD and vascular pathologies.

Introduction

Vascular cognitive impairment (VCI) from cerebral small vessel disease (CSVD) and Alzheimer's disease (AD) are common causes of age-related cognitive decline. Simplistically, CSVD affects white matter [1], while AD pathology leads to gray matter atrophy [2]. However,

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CVSD can drive cortical atrophy and AD can affect white matter through incompletely understood mechanisms [3, 4]. Further, they often coexist but can be difficult to clinically distinguish at early stages [5]. Prodromal differentiation of AD-, CSVD-related, or mixed cognitive decline can help guide therapeutics and prognosis, as phenotype, comorbidities, and mortality may differ [6]. We previously showed in a neuropathology subsample from the National Alzheimer's Coordinating Center (NACC) that differences in neuropsychiatric measures between CSVD and AD emerge at mild dementia rather than mild cognitive impairment (MCI) [7], emphasizing a potential early role in adjunctive diagnostics such as neuroimaging.

In AD, radiographic atrophy of medial temporal lobe structures may be evident during prodromal stages [8]. Early CVSD-related cognitive impairment can show subcortical white matter ischemic lesions and frontal lobe atrophy [9]. Qualitative visual assessment of temporal lobe atrophy on MRI may help distinguish AD from normal aging, VCI [10, 11], or other neurodegenerative processes at later clinical stages, but potentially suffers from lower interobserver agreement [12]. Quantitative volumetric analysis may provide greater reliability and accuracy [13]. It may also be useful in evaluating more global structural changes in early amyloid and CVSD pathologies, besides infarct or hemorrhage. Studies comparing volumetry between VCI and AD have not found a specific difference at either MCI or more cognitively impaired stages [14–17], but involved clinically diagnosed participants who may exhibit overlapping pathologies.

Using MRI brain volumetric analysis in a neuropathologically confirmed cohort from the NACC, we sought to evaluate volumetric differences in white matter hyperintensities (WMH) and cortical volumes of the frontal and temporal lobes at MCI between those with cerebral arteriolosclerosis alone (pARTE), AD alone (pAD), and mixed AD and arteriolosclerosis (ADARTE). We hypothesized that AD-related pAD and ADARTE would have smaller temporal lobe volumes and vascular-related pARTE and ADARTE would exhibit greater WMH and smaller frontal lobe volumes.

Methods

Participants

This cross-sectional analysis included data from NACC. Trained personnel at Alzheimer's Disease Research Centers (ADRC) throughout the USA enroll subjects ranging from cognitively normal to demented and collect longitudinal data for NACC using a Uniform Data Set (UDS). Respondents are the participant and coparticipants. Diagnoses are made by a team consensus or single physician [18]. Consenting participants also undergo a neuropsychological battery administered by a trained researcher. A subset of NACC patients have MRI brains with volumetric analysis conducted by the Imaging of Dementia and Aging (IDeA) Lab (Director: Charles DeCarli, MD; University of California, Davis; http://idealab.ucdavis.edu/), following Alzheimer's Disease Neuroimaging Initiative (ADNI) protocols [19]. An overlapping subset of participants consented to brain donation upon death and underwent autopsy to comprise the neuropathology dataset [20].

We acquired NACC data for all participants who had (1) neuropathology and (2) an MRI brain with volumetric analysis within 1 year of an UDS evaluation in which the subject had a Global Clinical Dementia Rating (CDR) score of 0.5, corresponding to MCI, using the CDR® Dementia Staging Instrument [21]. There were 318 participants who met these criteria with a total of 403 MRI brains with volumetric analysis performed between 2005 and 2017.

Neuropathology Groups

We excluded all participants with cortical ischemic infarcts, CADASIL, intracranial hemorrhages, and other neurodegenerative processes including Lewy body disease, frontotemporal dementia and other cerebral tauopathies, multiple system atrophy, and prion disease, such that the only major neuropathologies in our groups were isolated to arteriolosclerosis and/or AD pathology. We then defined three neuropathology groups: (1) pure arteriolosclerosis (pARTE) had only moderate-to-severe arteriolosclerosis, (2) pure AD (pAD) had only National Institute on Aging-Alzheimer's Association ABC score for AD of 2–3, and (3) AD with arteriolosclerosis (ADARTE) had both moderate to severe arteriolosclerosis and ABC score 2–3.

Neuropathological assessments in the NACC database are made by sampling all gross lesions and a minimum sampling of 13 brain regions with hematoxylin and eosin stains, based on reproducible procedures [22]. Arteriolosclerosis is defined as concentric hyaline thickening of the media of arterioles with possible intimal fibrosis. Global arteriolosclerosis severity is judged qualitatively on a scale of none, mild, moderate, or severe. AD pathology is further assessed with immunohistochemistry (preferred), Thioflavin S, or sensitive silver histochemical stains to derive an ABC score by ranking Ab plaque score, Braak neurofibrillary tangle stage, and CERAD neuritic plaque score. ABC scores range from 0 to 3, with scores 2 and 3 as intermediate and high AD pathology considered as sufficient explanation for dementia.

After forming neuropathology groups, there were 109 participants with volumetric analysis of a brain MRI within 1 year of an UDS evaluation with CDR 0.5. These participants were enrolled from 12 different ADRCs. If a participant had multiple qualifying MRIs, we used the last MRI at CDR 0.5 for cross-sectional analysis.

MRI Procedures and Volumetry

MRI scans at NACC are voluntarily submitted by ADRCs. Imaging data collection and acquisition protocols vary by ADRC. NACC began MRI collection in 2005. Submitted MRIs may include T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR) or other sequences and any combination thereof.

The IDeA Lab conducted volumetric MRI quantification for NACC based on ADNI 2 protocols, which is fully described at https://www.alz.washington.edu/WEB/adni_proto.pdf. Briefly for WMH, T2 FLAIR sequences were used. After excluding nonbrain

Table 1. Baseline characteristics by neuropathology groups

Characteristics	pARTE (*n* = 18)	pAD (*n* = 36)	ADARTE (*n* = 55)	*p* value
Age at MRI, years	83 (8)*	77 (10)*	80 (8)	0.04
Age at first noted cognitive decline, years	83 (7)^	72 (11)	74 (9)	<0.01
Age at death, years	87 (7)	82 (10)	85 (8)	0.05
Time from MRI to autopsy, years	4 (3)	5 (3)	5 (3)	0.10
Male sex	12 (67)	21 (58)	32 (58)	0.80
White	12 (67)^	34 (94)	50 (91)	0.01
Education, years	14 [12–16]	16 [13–18]	16 [12–18]	0.36
Any *APOE4* allele	3 (17)*	15 (42)	29 (53)*	0.02
Right-handed	16 (89)	34 (94)	50 (91)	0.82
Comorbidities				
Hypertension	14 (78)	22 (61)	39 (71)	0.41
Diabetes	6 (33)^	0 (0)	5 (9)	<0.01
Hyperlipidemia	13 (73)	19 (53)	35 (64)	0.34
Stroke/TIA	3 (17)	3 (8)	15 (27)	0.08
Any smoking	12 (67)	18 (50)	33 (60)	0.45
Depression	2 (11)	8 (22)	18 (33)	0.16

Age displayed as mean years (standard deviation). Education displayed as median years [interquartile range]. pARTE, pure arteriolosclerosis; pAD, pure Alzheimer's disease; ADARTE, mixed Alzheimer's disease and arteriolosclerosis; *APOE4*, apolipoprotein E allele 4; TIA, transient ischemic attack. * Post hoc Bonferroni $p < 0.05$ between groups. ^ Post hoc Bonferroni $p < 0.05$ from all other groups.

structures, FLAIR sequences are transformed to a high-resolution 3D T1 sequence using linear image registration, and then inhomogeneity between the native T1 and transformed T1 sequences is corrected for using nonlinear transformation that includes a multiple iteration interleaved bias estimation, B-spine deformation, and local histogram normalization method [23]. The transformed T1 sequence is then aligned to a common template atlas and WMH are calculated based on a Bayesian probability structure [24]. WMH segmentation is then performed by evaluating probability likelihood values of WMH at each white matter voxel.

Segmentation of the MRIs into gray matter, white matter, and CSF is achieved first through an Expectation-Maximization algorithm, which iteratively produces segmentation estimates and outputs from native T1 images [24]. This automated algorithm is based on the estimates from T1 templates used in WMH detection where the location of different tissues can be easily identified. Mean and standard deviation intensities of each tissue type are calculated and used as initial parameters for the automated segmenter, which undergoes multiple iterations with a Markov Random Field model that computationally refines the segmentation based on input intensities and image smoothness statistics. This automated process has high validity and inter-relater reliability when compared to manual segmentation by trained neuroradiologists [25]. From the final output, voxels determined from WMH segmentation are applied to create a final four tissue segmentation that is used in calculations. Measurements are reported in native space as volumes in cubic centimeters.

In our included subsample, all MRI studies had T1 images. There were 8 MRI studies without T2 FLAIR sequences and thus did not have WMH calculations (pAD = 5, ADARTE = 3). All studies that underwent volumetric analysis were acquired from a 1.5 or 3.0 Tesla MRI based on ADNI 2 protocols.

Statistical Analysis

All statistical analyses were performed with SPSS version 25 (IBM Corp, Armonk, NY, USA). We compared demographics, vascular risk factors, and apolipoprotein E allele 4 (*APOE4*) carrier status across neuropathology groups. Subjects were dichotomized as either *APOE4* carrier or noncarrier. For categorical variables, we used Pearson χ^2 and applied post hoc pairwise categorical comparisons using Bonferroni corrections. For continuous variables, we used one-way ANOVA with Tukey's post hoc test or Kruskal-Wallis *H* test with post hoc Dunn's test and Bonferroni adjustment to compare baseline characteristics and neuropsychiatric measures across neuropathology groups. We then conducted multinomial logistic regression to determine association between volumetric predictors of total WMH, frontal lobe, and temporal lobe volumes and neuropathology groups with pARTE as reference, adjusting for age at MRI and total cranial volume of cerebrum. Other potential confounders of race, *APOE4* carrier, and diabetes did not significantly impact the model in sensitivity analyses and, therefore, were not included. To correct for multiple comparisons, we applied Bonferroni correction based on 5 comparisons to *p* values. Adjusted *p* values of less than or equal to 0.05 were considered statistically significant.

Results

Participant Characteristics

Of 109 included participants, the mean age was 79 ± 9 years, 60% were male, and 88% white. Table 1 shows baseline characteristics by neuropathology groups. The pARTE group was older than pAD and had fewer *APOE4* car-

Table 2. Neuropsychiatric measures at MRI by pathology groups

Characteristics	pARTE (*n* = 18)	pAD (*n* = 36)	ADARTE (*n* = 55)	*p* value
MMSE	25 (23–28)	26 (24–27)	26 (24–28)	0.28
Logical memory IA	9 (5)	7 (4)	8 (4)	0.46
Logical memory IIA	7 (3–12)	4 (0–8)	3 (1–7)	0.35
Forward digit span	7 (2)	8 (2)	8 (2)	0.16
Backward digit span	4 (2)	5 (3)	6 (2)	0.21
Animals	12 (3)	14 (4)	13 (5)	0.58
Vegetables	9 (3)	9 (3)	8 (4)	0.40
Trail making test part A	56 (33–112)	50 (38–77)	57 (38–77)	0.42
Trail making test part B	119 (97–212)	161 (116–300)	180 (116–291)	0.44
WAIS-R digit symbol	28 (16)	31 (13)	29 (11)	0.71
Boston naming test	23 (17–26)	26 (23–27)	24 (19–27)	0.27
Geriatric depression scale	2 (1–3)	1 (1–2)	2 (0–4)	0.08

pARTE, pure arteriolosclerosis; pAD, pure Alzheimer's disease; ADARTE, mixed Alzheimer's disease and arteriolosclerosis; MMSE, Mini-Mental State Exam; WAIS-R, Wechsler Adult Intelligence Scale-revised.

Table 3. Adjusted logistic regression of volumetrics (reference pARTE)

Structure	pAD			ADARTE		
	aOR	95% CI	adjusted *p* value	aOR	95% CI	adjusted *p* value
Total brain WMH	0.94	0.90–0.98	0.02	0.96	0.93–0.99	0.04
L frontal lobe cortical	1.01	0.93–1.11	1.00	1.04	0.96–1.13	1.00
R frontal lobe cortical	1.06	0.97–1.17	1.00	1.10	1.01–1.22	0.20
L temporal lobe cortical	0.91	0.79–1.05	1.00	0.92	0.80–1.05	1.00
R temporal lobe cortical	0.86	0.74–1.00	0.25	0.83	0.72–0.96	0.05

Adjusted for age at MRI and total cerebral cranial volume. pARTE, pure arteriolosclerosis; pAD, pure Alzheimer's disease; ADARTE, mixed Alzheimer's disease and arteriolosclerosis; aOR, adjusted odds ratio; CI, confidence interval; L, left; R, right; WMH, white matter hyperintensities. *p* value adjusted by Bonferroni correction.

riers than ADARTE. Compared to both groups, pARTE had fewer white participants and a higher prevalence of diabetes. Neuropsychiatric profiles were similar between the neuropathology groups (Table 2). The total cerebrum cranial volume was similar between neuropathology groups (pARTE = 1,157 ± 117 cc, pAD = 1,207 ± 124 cc, ADARTE = 1,230 ± 143 cc, $p = 0.13$). Raw volumetry by neuropathology groups is shown in the online supplementary Table (for all online suppl. material, see www.karger.com/doi/10.1159/000524499).

Logistic Regression Analysis

We applied regression models to compare predictors of WMH, frontal, and temporal lobe volumes and neuropathology groups with pARTE as reference (Table 3). After adjustment for age at MRI and total cerebrum cranial volume, we find that AD-related groups were associated with less WMH volume (pAD adjusted odds ratio (aOR) (95% confidence interval [CI]): 0.94 (0.90–0.98), ADARTE aOR (95% CI): 0.96 (0.93–0.99)) than pARTE. The ADARTE, but not pAD group, had larger right frontal cortex volumes than pARTE (pAD aOR [95% CI]: 1.06 [0.97–1.17], ADARTE aOR [95% CI]: 1.10 [1.01–1.22]). Similarly, the mixed pathology group, but not pAD, had significantly smaller right temporal lobe volumes than pARTE (pAD aOR [95% CI]: 0.86 [0.74–1.00], ADARTE aOR [95% CI]: 0.83 [0.72–0.96]). The differences in WMH and right temporal lobe volumes remained significant after Bonferroni correction.

Discussion

In this neuropathologically confirmed subsample from NACC, we found volumetric differences in WMH and temporal lobe volumes between Alzheimer- and CVSD-related MCI. When comparing temporal lobe volumes against pARTE, it appeared that the mixed pathology group had a greater association with atrophy than pAD, suggesting an early additive effect of Alzheimer and vascular processes on gray matter degeneration. In prior studies, it has been difficult to discern volumetric differences between early AD and VCI [15, 17], partly owing to limitations in clinical diagnostic classification of these entities. This study adds novelty with a neuropathologically confirmed cohort.

We found that the pure vascular pathology group had a greater WMH volume than their AD-related counterparts, consistent with other clinically diagnosed dementia cohorts [26, 27]. WMH of presumed vascular origin are known neuroimaging features of CVSD-related brain changes [28]. Accordingly, those with the greatest vascular burden to reach MCI in our study, the pARTE group, would expectedly have greater WMH volumes. Though WMH frequently exist in individuals with AD [29], they are more strongly linked to VCI risk than AD risk and may predict progression from MCI to dementia [30]. Multifactorial evaluation of CVSD-related brain changes including WMH volume, lacunes, and gray matter atrophy may help determine cognitive and functional outcomes in VCI [31]; therefore, further refinement of a continuously measured WMH volume or establishing volume thresholds for a predictive model may be useful in the prodromal stage.

Though WMH are increasingly recognized to be involved in AD, their exact relationship with Alzheimer pathology is not entirely known [32]. White matter ischemia has been previously associated with hippocampal volume loss [33]. Diffusion tension imaging studies have found distinct patterns of cortical atrophy, including in the temporal lobe, related to white matter microstructure [4]. We found that the mixed pathology group was associated with smaller temporal lobe volumes when compared to pARTE, but not as strong of a relationship between pAD and pARTE. This may suggest an additive effect of Alzheimer pathology and cerebral arteriolosclerosis on early temporal cortical atrophy. Previously, it has been demonstrated that AD and CVSD can converge to cause similar gray matter atrophy [33]. Our findings suggested that this may be seen as early as MCI, though it is unclear if WMH are involved in this pattern, as we found no difference in WMH volume between pAD and ADARTE.

The reason for right- rather than left-sided findings is also not clear. Prior reports have described asymmetry in hippocampal atrophy during AD, which may vary in laterality by clinical stage or *APOE4* allele [34, 35]. AD pathology may not be completely uniform throughout the brain [36]; however, these prior reports do not fully consider coexistent vascular pathology, which may also influence atrophy patterns. Our present data do not capture WMH topography, subtle white matter tract injury, or distribution of arteriolosclerosis burden, which may be relevant in the complete pathophysiological pathways of temporal lobe atrophy in early AD [4, 37]. Laterality of atrophy may be an important consideration in prodromal psychometric testing, as certain tests may be less sensitive for nondominant hemisphere functions. We found no differences in neuropsychiatric measures in this analysis or our previous study at MCI [7], but the available measures may not best reflect right temporal lobe changes [38].

Lastly, we did not find a strong relationship between frontal lobe volume and neuropathology groups. Previously, frontal lobe subregion atrophy has correlated with worsened cognitive performance in those with significant WMH [39]. Possibly, more global frontal lobe changes in CVSD are not as evident until later cognitive stages [40]. Frontal lobe atrophy rates may also be important in predicting cognitive course in those with CVSD [41].

Strengths of this study include the use of an autopsy-confirmed cohort, which can add diagnostic certainty to our comparisons. Weaknesses include the cross-sectional design and limitations in generalizability. Given the cross-sectional nature, we are unable to assess dynamic temporal contributions of pathologies as participants age. Though from a nationwide multicenter database, certain populations may be more likely to enroll from tertiary care centers, participate in a research study, and consent for autopsy, which may be reflected by the predominantly white and higher education composition of our sample. Further, selection of pure pathology may not reflect community pathology, which is probably more heterogeneous and therefore multifactorial in brain atrophy. A relatively smaller sample also limits our analytic precision in comparing smaller subregions.

In conclusion, we identified volumetric differences at MCI in WMH and temporal cortex volumes between neuropathologically confirmed pARTE, pAD, and mixed pathologies in a subsample from NACC. In both findings, CVSD-related pathology appeared to contribute substan-

tially to brain changes at this early clinical stage. In particular, the right versus left temporal lobe appears particularly susceptible to mixed pathology. Given the known impact of CVSD on cognitive impairment, including in AD [32], this additionally highlights the importance vascular risk factor management during the prodromal stage. Further research in a larger cohort is needed to discern clinical utility in early volumetric changes and pathophysiological mechanisms underlying patterns of atrophy between VCI, AD, and their combination.

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Statement of Ethics

Data were obtained from NACC. The study protocol was reviewed and the need for approval was waived by the University of Washington Human Subjects Division because it does not involve human subjects, as defined by Federal and State Regulations. All contributing ADRCs are required to obtain informed consent from participants and to maintain their own separate IRB review and approval from their own institution prior to submitting data to NACC.

Conflict of Interest Statement

Dr. Arjun Masurkar is on the Steering Committee of the Alzheimer Disease Cooperative Study and is a council member for the Alzheimer's Association International Research Grants Program. Dr. Dixon Yang has no conflicts of interest to disclose.

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Author Contributions

Dr. Dixon Yang: study design, data acquisition, analysis and interpretation, and drafting the work. Dr. Arjun Masurkar: study design, interpretation, and critical revision.

Data Availability Statement

Data for this study were obtained from NACC where restrictions may apply. Inquiries for data sharing should be directed toward NACC via https://naccdata.org/requesting-data/submit-data-request.

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