Cerebral Amyloid Angiopathy Patients Exhibit Cortical Gray Matter Atrophy but Not Hypoperfusion

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Target Audience: Clinical researchers interested in cerebral amyloid angiopathy and vascular cognitive impairment

Purpose: Cerebral amyloid angiopathy (CAA) is caused by vascular beta-amyloid deposition and is diagnosed clinically on the basis of intracerebral hemorrhages and cerebral microbleeds. However, it is also associated with microinfarcts, white matter hyperintensities of presumed vascular origin, and compromised vascular reactivity [1]. Pseudo-continuous arterial spin labeling (pCASL) is a technique for non-invasive quantitative cerebral blood flow (CBF) measurements with MR [2]. Alzheimer's disease (AD) is marked by focal hypoperfusion, as measured with pCASL [3], of brain regions that exhibit hypometabolism on FDG-PET [4]. We hypothesize that CAA patients will exhibit reduced resting perfusion and lower cortical gray matter volumes in the occipital lobe, which tends to be most heavily affected by vascular amyloid.

Methods: As part of a prospective longitudinal cohort study, probable CAA participants were diagnosed using the Boston criteria [5] and were recruited from the stroke unit and dementia clinics; AD patients and mild cognitive impairment (MCI) patients were diagnosed by consensus NIA-AA research criteria [6,7] using clinical data without pathophysiological biomarker support and were recruited from a dementia clinic; and healthy controls (HC) were recruited through poster advertisements in the community. CAA participants were identified based on the following initial complaints/symptoms: intracerebral hemorrhage (ICH, *n*=14), cognitive complaints (*n*=7), transient focal neurological symptoms (*n*=3), headache (*n*=2), or as an incidental MR finding (*n*=3), or other. Participants with evidence of CAA-related inflammation (*n*=4) were imaged while in remission. All participants underwent multi-modal MR examinations on a 3T magnet (GE Healthcare Discovery 750, Waukesha, WI); relevant acquisitions were: (1) T1-weighted high-resolution (1 mm^3) 3D anatomical data set; (2) T2-weighted fluid-attenuated inversion recovery (FLAIR); and (3) full-brain background-suppressed pCASL acquisition with 1500 ms label duration with 1525 ms post-label delay (PLD) [2]. FSL was used to coregister the pCASL and T1 data [8]. Using the MNI152 atlas in FSL, GM regions-of-interest (ROIs) were derived for CBF and GM volumetric analysis (Table 1); total intracranial volume, total hemispheric GM and white matter (WM) volume were also recorded. The GM ROIs included a meta-ROI comprised of portions of the angular gyrus, lateral temporal lobe, and posterior cingulate known to exhibit decreased perfusion [3] and metabolism [4] in AD (AD-ROI). Hemispheres with ICH >10 mm diameter were excluded, and analyses were performed on each cerebral hemisphere independently. The occipital lobe:global and AD-ROI:global CBF data were analyzed to compare CAA to the other three groups using linear mixed models, using the Dunnett-Hsu method to control for multiple comparisons, with a random effects term to account for clustering of hemispheres within participants. Models were adjusted for age and history of hypertension. Volumetric ROI data were normalized to an average intracranial volume of 1,488.9 mL to account for individual differences in head size and then analyzed in a similar fashion, controlling for age and sex. SAS v9.3 (Cary, NC) was used for statistical analyses.

Results: Sixty-nine (69) participants were included in this cross-sectional analysis: 29 CAA (10 F, mean 74.0 ± 6.9 years, 45 hemispheres included and 13 excluded due to ICH), 18 HC (9 F, mean 67.0 ± 10.3 years,), 11 AD (3 F, mean 66.6 ± 5.9 years,), and 11 MCI (6 F, mean 72.1 ± 7.5 years). After adjusting for age, hypertension, and clustering of hemispheres within patients, no significant difference was observed between CAA and any of the other groups in occipital perfusion, AD-ROI perfusion, or in either CBF ratio. However, CAA patients had lower GM volume than controls in all brain lobes except the temporal lobe and HC, but higher WM (Table 1).

		HC	MCI	AD	CAA
Volume (mL)	Hemis. GM	****210.9 ± 3.3**	201.9 ± 4.2	195.4 ± 4.3	194.5 ± 2.8
	Hemis. WM	****211.3 ± 2.8**	****209.0 ± 3.5**	****207.6 ± 3.6**	223.5 ± 2.3
	Hippocamp	2.8 ± 0.1	2.9 ± 0.1	2.7 ± 0.1	2.8 ± 0.1
	Frontal GM	***49.9 ± 1.0**	46.1 ± 1.2	47.5 ± 1.3	46.0 ± 0.9
	Occipital GM	***17.0 ± 0.4**	16.2 ± 0.5	14.9 ± 0.5	15.5 ± 0.4
	Parietal GM	****33.1 ± 0.7**	31.2 ± 0.9	30.3 ± 0.9	30.0 ± 0.6
	Temporal GM	37.7 ± 0.8	36.9 ± 1.0	34.0 ± 1.0	35.7 ± 0.7
CBF (mL/100g/min)	Hemis. CBF	39.3 ± 2.5	35.7 ± 3.0	31.4 ± 2.8	35.6 ± 2.0
	Occipital CBF	36.7 ± 3.5	37.3 ± 4.2	28.2 ± 3.9	34.0 ± 2.7
	AD-ROI CBF	46.7 ± 3.5	42.7 ± 4.1	29.6 ± 3.9	38.0 ± 2.7
CBF Ratio	Occip.:Hemis.	0.89 ± 0.04	0.95 ± 0.05	0.84 ± 0.04	0.89 ± 0.03
	AD-ROI:Hemis.	1.15 ± 0.04	1.13 ± 0.05	0.94 ± 0.04	1.05 ± 0.03

Table 1: Model-estimated CBF (mL/100g/min) and GM Volume Measurements (mL) in CAA, AD, MCI and HC (Hemis. = Hemispheric, Hippocamp. = Hippocampus) No significant differences were seen in the CBF measurements between CAA and the other groups. Significant differences were seen in the GM volumes in the regions shown above. P-values are relative to CAA; *, P < 0.01; and **, P < 0.005.

Discussion: We observed lower GM volume in CAA than controls, indicative of cortical GM atrophy. However, contrary to our hypothesis we did not find significant differences in resting perfusion in CAA. This is consistent with a previous study that used ASL MR imaging to look at resting perfusion in the occipital lobe only [9]. Unexpectedly, we observed higher WM in CAA than the other groups, possibly consistent with vasogenic white matter edema. Higher WM volumes have recently been described in another small vessel disease, CADASIL that also causes white matter injury [10]. Future work will seek to identify risk factors for, consequences of, and the longitudinal course of GM atrophy and WM hypertrophy in CAA.

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