White Matter Alterations in Cerebral Amyloid Angiopathy Measured by Diffusion Tensor Imaging

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Background and Purpose—Cerebral amyloid angiopathy (CAA) represents β-amyloid deposition in the small- and medium-sized vessels of the brain and meninges. CAA contributes to altered vessel function and is associated with white matter damage, cognitive impairment, and most salient, hemorrhagic stroke. We used diffusion tensor imaging to evaluate the anatomic distribution of white matter degeneration in participants diagnosed with advanced CAA.

Methods—Diffusion tensor imaging was obtained from 11 participants diagnosed with CAA-related intracerebral hemorrhage and 13 matched healthy control participants. Fractional anisotropy (FA) and diffusivity maps were compared using voxel based t-test and region-of-interest analyses.

Results—FA was reduced in CAA in temporal white matter and in the splenium of the corpus callosum (P<0.001 with 17% reduction in temporal white matter and 15% reduction in the splenium). FA was marginally increased in CAA in the posterior limb of the internal capsule and subthalamic gray matter regions (7% increase in subthalamic gray). FA changes were bilateral, remained significant in cluster analysis controlling for multiple comparisons, and did not depend on the hemisphere of the cerebral hemorrhage. Diffusivity was not substantially altered.

Conclusions—These findings suggest that a pattern of regional brain tissue degeneration is a characteristic feature of advanced CAA. (Stroke. 2006;37:1759-1764.)

Key Words: aging • amyloid • cerebral hemorrhage • dementia • diffusion

Cerebral amyloid angiopathy (CAA) is defined by the deposition of β-amyloid in the media and adventitia of small- and medium-sized cortical and meningeal vessels. Advanced CAA can lead to vessel fragility and rupture with resulting intracerebral hemorrhage (ICH) in the corticocortical (lobar) regions of the brain. CAA can be diagnosed with high specificity by the presence of multiple hemorrhages (including asymptomatic microbleeds detected on gradient-echo MRI) restricted to lobar locations.

Recent data suggest that CAA contributes to cognitive impairment independent of its effects on brain hemorrhage and its known association with Alzheimer-type pathology. White matter lesions, typically caused by ischemic insult, are frequent in patients with probable CAA and are more severe in individuals with cognitive impairment. There is a correlation between the extent of the white matter lesions and the number of lobar hemorrhages, and there is a suggestive correlation between the posterior predominance of both the vascular pathology and the periventricular white matter hyperintensities (WMH) in CAA. It is thus possible that vascular dysfunction and subsequent ischemic white matter damage contribute to cognitive decline in CAA.

A sensitive measure of white matter structure could be useful in determining the extent and topography of CAA-related pathology. Recent studies have used diffusion tensor imaging (DTI) to map subtle brain changes associated with aging and neurological disease. We used DTI to determine the regional pattern of white matter disruption in CAA and hypothesized that white matter integrity would be most severely reduced in posterior brain regions, where vascular pathology in CAA is suggested to be most prominent.

Materials and Methods

Participants

Images were obtained from 24 participants: 13 nondemented older adults without history of stroke (CON; mean age 66.7±3.0 years; 5 male/L/8 female) recruited through the Harvard Cooperative Program on Aging and 11 patients with lobar ICH and probable CAA (CAA; mean age 71.7±1.9 years; 4 male/L/7 female) recruited through the Massachusetts General Hospital Stroke Unit. Participants fulfilled the Boston Criteria for probable CAA when multiple...
symptomatic or asymptomatic lobar ICHs were present on gradient-echo MRI. A prior validation study of these criteria demonstrated moderate to severe CAA pathology in 13 of 13 patients diagnosed with probable CAA. Eight of the 11 CAA participants had intact cognition, defined by Mini-Mental Status Examination (MMSE) score ≥ 27 and Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-COG) ≤ 13; 3 had mild cognitive deficits (MMSE 23 to 27). CON were excluded if they had a history of neurological or psychiatric disorder, or serious cardiovascular disease. Cardiovascular risk factors were uncommon in CAA and CON (CAA: 2 with hypertension; CON: 2 with hypertension, 1 on lipid-lowering medication, 1 with diabetes mellitus). CON had no history of stroke or hemorrhage on conventional MRI. All participants provided written informed consent.

MRI
Participants received a high-resolution DTI scan (Siemens; 1.5 Tesla Sonata System; repetition time [TR]=8.4 or 9.0 seconds and echo time [TE]=71 or 68 ms, slice thickness=2 mm [no gap], 60 slices total, acquisition matrix 128×128 [field of view=256×256 mm], 8 averages, 6 noncollinear directions with b value=700 seconds/mm², and one T2-weighted image, with b value=0 seconds/mm²). Acquisitions used a twice-refocused balanced echo to reduce eddy current distortions. CAA also received a fluid-attenuated inversion recovery (FLAIR) scan for identification of WMH (TR=7.5 seconds, flip angle=150°, slice thickness/gap=5/1 mm, 23 slices, acquisition matrix 384×512, field of view 22×22 cm) and gradient-echo sequences (TR=7.5 seconds, echo time=25 ms, flip angle=25°, slice thickness/gap 5/1 mm) to identify sites of previous hemorrhages. Hemorrhagic lesions were counted and marked with centroids.

Image Analysis
DTI data were processed using a multistep procedure, and voxel-based and manual region-of-interest (ROI) comparisons of fractional anisotropy (FA) values were performed. These analyses excluded hemorrhagic regions through masking out regions with very low anisotropy (<0.2) and high trace values (>0.006 mm²/second). Each of these steps is described in detail elsewhere and briefly below.

Preprocessing
Data were processed using the Freesurfer (http://surfer.nmr.mgh.harvard.edu) and FSL (http://www.fmrib.ox.ac.uk/fsl) processing streams. A T2-weighted structural volume, collected using identical sequence parameters as the directional volumes with no diffusion-weighting and thus in register with the final diffusion maps, was used for all registration and motion correction using a 12-parameter affine mutual information procedure in FMRIB’s Linear Image Registration Tool (FLIRT). The diffusion tensor was calculated for each voxel using a least-squares fit to the diffusion signal. The FA metric was derived from the diffusion tensor as described.

Whole-Brain Maps
Spatially normalized FA and diffusivity maps were smoothed using a 3-D filter with a full width at half maximum of 6 mm and CON and CAA were compared by t test at each voxel. Results were considered exploratory because of the potential for registration misalignment to contribute to statistical results in whole-brain voxel-based studies, and regions showing significant differences in these analyses were confirmed with manual measurements.

WMH Segmentation
Manual segmentation of FLAIR images to obtain WMH normalized to head size (nWMH) was performed with MRicro software (www.mricro.com) by 2 blinded raters (E.E.S., M.E.G.) This method provides high inter-rater reliability (intraclass correlation coefficient=0.98). To avoid confounding by the presence of focal white matter damage attributable to prior ICH, we analyzed nWMH only in the hemisphere not affected by ICH.

Regional Analyses
Regions for ROI analyses were selected in areas showing statistical effects in the voxel-based maps and control regions that were unaffected in the voxel-based maps, and included temporal white matter, the anterior and posterior limb of the internal capsule, and the genu and splenium of the corpus callosum. ROIs were placed in spatially normalized images by a single rater blinded to participant demographics. The temporal ROI was defined as a region in the
temporal stem in the coronal image where the third ventricle is most narrow, then choosing a point where the stem intersects with the superior temporal gyrus and placing a line of ~10 voxels in the sagittal view. The subthalamic region was drawn on the same coronal slice as a line of 5 to 10 voxels beginning superiorly at the point at which the thalamus curves inward at the level of the mediodorsal/centromedial nuclei and ending inferiorly just before the cerebral peduncles. The internal capsule was placed in an axial slice at the level of the point where the thalamus meets the subthalamic gray matter in the coronal plane. Callosal ROIs were placed in the central portion of the genu and splenium in the midsagittal plane. ROI placement was performed using both the FA and trace volumes.

Statistical Analyses

Data were compared by unpaired t tests (P<0.05 was considered statistically significant for this exploratory analysis). Multiple comparisons control was performed at the cluster level using the Monte Carlo permutation test.20 This procedure provides a statistical value based on the probability of a regional statistical cluster given random mixing of participants from the total subject sample. The null distribution for cluster size was computed for each voxel using a cluster threshold of P<0.005 and 18-neighbor connectivity. The corrected cluster significance was then determined as the median of the corrected voxel-level significance values within each cluster using 103 trials. The nWMH volumes were log-transformed to achieve a normal distribution and the association between nWMH and splenium in the midsagittal plane. ROI placement was performed where the thalamus meets the subthalamic gray matter in the coronal plane. ROIs were used to confirm the findings and the location of hemorrhages in pooled analysis.

Results

Voxel analyses demonstrated several suggestive regions of altered FA in CAA compared with controls (Figure 1), including temporal white matter, the splenium of the corpus callosum, and lateral frontal white matter. FA was increased in CAA in a portion of the posterior limb of the internal capsule and in subthalamic gray matter (Figure 1). There was additionally an increase in FA in the frontal white matter where superior longitudinal and corticospinal fibers intersect. Regions remained significantly different (P<0.05) between CAA and CON after permutation tests controlling for multiple comparisons. Statistically altered regions could be visually detected in group averaged anisotropy maps as well as maps from individual participants (Figure 2). Maps of mean diffusivity (MD) showed minimal differences between CAA and CON, except in subthalamic gray matter superior to the area of increased FA (data not shown).

Regional Analyses

Manually placed ROIs were used to confirm the findings from the voxel-based maps. Analyses confirmed reductions in FA with CAA in the splenium of the CC and temporal white matter bilaterally (P<0.001), with lesser reduction in the genu of the CC (P<0.05) and no change in the anterior limb of the internal capsule (Figure 3; Table). The increases were confirmed in the posterior limb of the internal capsule (P<0.01) and in the gray matter ventral to the thalamus (P<0.01 on left; P=0.08 on right). Findings in the splenium, temporal white matter, and left subthalamic gray matter remained significant with a Bonferroni correction of ROI data for 6 independent comparisons. To ensure that placement of the initial ROIs was not biased by information from the FA maps, we performed a second set of ROI analyses in the temporal, subthalamic, and callosal regions using the trace volume for regional placement. This analysis confirmed a similar pattern of alterations (P<0.01 in temporal WM bilater-

![Figure 2](http://stroke.ahajournals.org/)

Figure 2. FA maps in CON and CAA. Brighter voxel intensity signifies higher FA values. Top panel, Spatially normalized voxel-based maps showing mean anisotropy averaged across all CON (left panel) and patients with CAA (right panel). Bottom panel, FA maps in a single representative CON participant (left panel) and patient with CAA. The average and individual images demonstrate a qualitative reduction in FA in temporal white matter in patients with CAA (white arrows) and an increase in FA in subthalamic gray matter (black arrows).

![CON vs CAA](http://stroke.ahajournals.org/)

CON CAA

ally, P<0.01 in subthalamic gray matter bilaterally, and P<0.05 in the genu and splenium of the corpus callosum).

The regional alterations in FA were present bilaterally, suggesting they were not driven primarily by the CAA-related ICH. We further explored this possibility by dividing participants based on the hemisphere containing the index ICH (Figure 4). Altered FA was apparent in both hemispheres regardless of whether the ICH was present in the left or right hemisphere, suggesting that the observed effects were not attributable to secondary post-ICH degeneration of underlying white matter. Additionally, the ipsilateral to contralateral anisotropy ratios did not differ significantly from 1 in any ROI.

We examined the correlation between nWMH volume and FA ROI values. Within CAA participants, there was a significant negative correlation between nWMH volume and the mean FA of combined white matter ROIs with reduced FA (r=-0.73, P=0.04). The regional pattern of WMH in coregistered images, however, did not show substantial overlap between the areas of altered FA and WMH, which favored frontal and occipital periventricular regions. Similarly, there was no substantial overlap between the areas of FA alterations and the location of hemorrhages in pooled analysis across the CAA participants (supplemental Figures I and II, available online at http://stroke.ahajournals.org). These observations suggest that alterations in FA among CAA participants were not a direct effect of other CAA-related radiological findings such as WMH or microhemorrhage, although it is possible that alterations not visible on clinical MRI could contribute to these results.
Discussion

We examined whether patients with CAA exhibit alterations in MRI measures in regions of normal appearing white matter without visually obvious lesions. Complimentary voxel-based and ROI analyses identified several areas of reduced FA, most prominent in the splenium of the corpus callosum, and temporal white matter. The affected temporal white matter appears confined to regions of the inferior longitudinal/occipital fasciculi. Both the splenium of the callosum and the inferior longitudinal/occipital fasciculi contain fibers projecting from occipital cortex, suggesting a possible association between the regions of reduced FA and the occipital predominance of CAA pathology.7,21,22 These regions of altered FA overlapped minimally with regions affected by WMH or microhemorrhage. Therefore, it is unlikely that the alterations observed are directly related to altered signal attributable to major tissue damage.

An alternative possibility is that the measured alterations in FA are secondary effects of other local CAA-related changes such as hemorrhage, WMH, or atrophy. Although we cannot exclude this possibility (the association between nWMH volume and overall FA suggests some relationship), we did not find evidence for a straightforward regional association between altered FA and these other lesion types. FA findings were bilateral (with contralateral:ipsilateral ratios close to 1), and there was no correlation between FA in any ROI and the ipsilateral, contralateral or total number of hemorrhages on

**Figure 3.** Scatterplots of regional FA measures in CAA and CON. ROIs were manually placed to confirm the findings from voxel-based analyses. CAA had significantly lower FA values in the splenium (S) and less difference in the genu (G) of the corpus callosum (top panel), and lower values in temporal white matter in the left (L) and right (R) hemispheres (middle panel). CAA had greater FA values in subthalamic gray matter bilaterally compared with CON (bottom panel).

<table>
<thead>
<tr>
<th>Region</th>
<th>CON</th>
<th>CAA</th>
<th>t value (P Value, uncorrected)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SEM</td>
<td>Mean ± SEM</td>
<td></td>
</tr>
<tr>
<td>Genu</td>
<td>0.66 ± 0.02</td>
<td>0.58 ± 0.03</td>
<td>-2.2 (0.042)</td>
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<tr>
<td></td>
<td>0.02 ± 0.03</td>
<td>0.03 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>Splenium</td>
<td>0.75 ± 0.01</td>
<td>0.64 ± 0.03</td>
<td>-3.6 (0.002)</td>
</tr>
<tr>
<td></td>
<td>0.01 ± 0.03</td>
<td>0.03 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>Temporal (L/R)</td>
<td>0.51/0.52 ± 0.01/0.01</td>
<td>0.42/0.43 ± 0.02/0.01</td>
<td>-4.7 (0.001)/-4.4 (0.001)</td>
</tr>
<tr>
<td></td>
<td>0.01/0.01 ± 0.02/0.01</td>
<td>1.8 (0.09)</td>
<td></td>
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<tr>
<td>Subthalamic (L/R)</td>
<td>0.39/0.41 ± 0.01/0.01</td>
<td>0.42/0.43 ± 0.01/0.01</td>
<td>3.3 (0.004)/1.8 (0.09)</td>
</tr>
<tr>
<td></td>
<td>0.01/0.01 ± 0.02/0.02</td>
<td>0.00/0.00</td>
<td></td>
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<tr>
<td>Anterior Limb (L/R)</td>
<td>0.54/0.55 ± 0.01/0.01</td>
<td>0.55/0.55 ± 0.02/0.02</td>
<td>0.6 (NS)/0.5 (NS)</td>
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<td></td>
<td>0.01/0.01 ± 0.02/0.02</td>
<td>0.01/0.01</td>
<td></td>
</tr>
<tr>
<td>Posterior Limb (L/R)</td>
<td>0.57/0.58 ± 0.01/0.01</td>
<td>0.61/0.62 ± 0.01/0.01</td>
<td>2.7 (0.013)/2.7 (0.013)</td>
</tr>
<tr>
<td></td>
<td>0.01/0.01 ± 0.01/0.01</td>
<td>0.01/0.01</td>
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NS indicates not significant.

**Figure 4.** Bar charts of regional FA measures in CAA and CON, with CAA split by the hemisphere of their intracerebral hemorrhage. The color of the label on the X axis denotes the group (the color of the bar) that would be expected to have a stronger effect if the changes in FA occurred preferentially ipsilateral to the ICH. The ipsilateral and contralateral similarities suggest that the regional changes in FA were attributable to a generic process of the disease and not secondary degeneration from the overlying hemorrhage.
gradient-echo MRI.\textsuperscript{13} We were not, however, able to analyze possible effects of hemorrhage volume, because this information was not available for all subjects. In the case of atrophy, we observed no significant correlations between whole-brain volume and ROI measures. The current study has only limited statistical power to detect such secondary relationships, however. The changes observed in the current study could also be a secondary effect of small nonvisible infarcts.

FA was increased in the posterior limb of the internal capsule and subthalamic gray matter with CAA. It is important to note that the biophysical features that contribute to regional FA are still relatively unknown. Findings of increased FA are therefore of great interest for pathological study to determine the factors causing these more rare increases. Also, although many studies have used DTI measures of FA with a focus on its exquisite white matter contrast, the FA metric is a more general marker of tissue structure for both gray matter and white matter. Others have reported increased FA in the basal ganglia with multiple sclerosis,\textsuperscript{23} potentially attributable to selective alteration of crossing fibers. Still, it is important to note that the findings of increased FA were less statistically robust than those of decreased FA, and thus, replication and further study of these patterns will be important aspects of future work. The majority of observed alterations in FA were not associated with significant changes in MD. Although decreased FA often occurs together with increased MD in areas of tissue damage such as acute demyelination\textsuperscript{9} or ischemic white matter,\textsuperscript{24} loss of anisotropy does not necessarily dictate increased diffusivity. Indeed, processes such as gliosis may decrease both diffusivity and anisotropy.\textsuperscript{25} Interestingly, a diffusion-weighted MR study of a mouse model for CAA and Alzheimer disease (AD) found decreased diffusivity,\textsuperscript{26} suggesting that the effects of amyloid deposition on this measure may be complex.

FA changes reported here qualitatively resemble patterns of white matter degeneration observed in AD.\textsuperscript{8,11} These similarities could reflect the high prevalence of CAA pathology in patients with AD, raising the possibility that vascular amyloid may be an important contributor to white matter changes in that disorder. Alternatively, it is possible that FA changes reflect atrophic or amyloid and tau-based pathologies associated with early AD as opposed to CAA. The current dataset was not statistically powered to detect associations between diffusion measures and cognitive scores, an important question for future study.

Limitations of the current study are being addressed in our current work. Manual ROI placement is potentially subject to operator bias. Future studies will use novel techniques for automated ROI placement using diffusion tractography. Scan sequences were slightly different between CAA and control participants. The sequence differences would be expected to influence the general signal-to-noise ratio rather than tissue properties such as FA. We also note that FA variance was similar between CON and CAA groups and the effects of CAA were very regionally specified. Thus, it is unlikely that the small differences in scan sequences contributed to the robust statistical results observed. The validity of the FA measurements in the CAA group is further supported by the correlation between FA and nWMH volume, a presumably independent measure of white matter change.

**Summary**

The results of this study suggest that DTI-based methods can detect a characteristic regional pattern of pathological changes in CAA that occur via mechanisms not directly related to ICH and ICH-related secondary degeneration. Population-based autopsy studies show that the prevalence of CAA greatly exceeds the prevalence of lobar hemorrhage.\textsuperscript{4} Thus, DTI could be a useful step toward measuring this “asymptomatic” pathology and determining how white matter degeneration contributes to cognitive impairment in CAA.

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**Disclosure**

None.

**References**


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