Evolution of DWI lesions in cerebral amyloid angiopathy

Evidence for ischemia

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ABSTRACT

Objective: To address the pathophysiologic nature of small diffusion-weighted imaging (DWI) lesions in patients with cerebral amyloid angiopathy (CAA) who underwent serial MRI. Specifically, we tested (1) whether DWI lesions occurred preferentially in individuals with prior DWI lesions, (2) the cross-sectional association with chronic cortical cerebral microinfarcts (CMIs), and (3) the evolution of DWI lesions over time.

Methods: Patients with probable CAA ($n = 79$) who underwent at least 2 MRI sessions were included. DWI lesions were assessed at each available time point. Lesion appearance and characteristics were assessed on available structural follow-up images. Presence and burden of other neuroimaging markers of small vessel disease (white matter hyperintensities, cerebral microbleeds, cortical superficial siderosis, and chronic cortical CMIs) were assessed as well.

Results: Among 221 DWI scans (79 patients with 2 DWI scans; 40 with ≥ 3), 60 DWI lesions were found in 28 patients. Patients with DWI lesions at baseline were not more likely to have additional DWI lesions on follow-up compared to patients without DWI lesions at baseline. DWI lesions were associated with chronic cortical CMIs and cortical superficial siderosis, but not with other markers. For 39/60 DWI lesions, >1 MRI sequence was available at follow-up to determine lesion evolution. Twenty-four (62%) were demarcated as chronic lesions on follow-up MRI. Five appeared as cavitations, 18 as noncavitated infarcts, and 1 underwent hemorrhagic transformation.

Conclusions: Based on their neuroimaging signature as well as their association with chronic cortical CMIs, DWI lesions appear to have an ischemic origin and represent one part of the CMI spectrum. **Neurology® 2017;89:2136–2142**

GLOSSARY

ADC = apparent diffusion coefficient; **CAA** = cerebral amyloid angiopathy; **CMB** = cerebral microbleed; **CMI** = cerebral microinfarct; **DWI** = diffusion-weighted imaging; **FLAIR** = fluid-attenuated inversion recovery; **GRE** = gradient-recalled echo; **ICC** = intraclass correlation coefficient; **ICH** = intracerebral hemorrhage; **MMSE** = Mini-Mental State Examination; **SWI** = susceptibility-weighted imaging; **WMH** = white matter hyperintensity.

Cerebral amyloid angiopathy (CAA) is common in old age, characterized by recurrent lobar intracerebral hemorrhage (ICH).¹ Neuroimaging studies have shown a broad spectrum of pathology in these patients, including white matter hyperintensities (WMHs), lacunes, and cerebral microbleeds (CMBs).^{2,3} More recently, small diffusion-weighted imaging (DWI) lesions have been described in up to 23% of CAA patients.^{4–6} These DWI lesions remain visible for only approximately 1–2 weeks,^{7,8} indicating that this high single time point proportion probably reflects a high incidence of lesions in these patients.⁹ Despite their high occurrence, little is known about their underlying etiology. Although some believe that DWI lesions represent acute small infarcts, evidence remains limited. It has even been suggested that they may be precursors of CMBs,¹⁰ which is not inconceivable in this bleeding-prone population.

We tested whether DWI lesions represent one aspect of the broader microinfarct spectrum. Cerebral microinfarcts (CMIs) are considered the most widespread form of brain infarction and

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are very common in CAA.¹¹ CMIs used to be only described on pathology, but recently it has become possible to visualize cortical CMIs with in vivo structural MRI.^{12,13} If DWI lesions are part of the CMI spectrum, we expect (1) DWI lesions to occur in a broad cross-section of CAA patients rather than a restricted subset, (2) an association with chronic cortical CMIs, and (3) at least a subset to evolve into cavitated lesions or T2 hyperintensities.¹⁴

METHODS Cohort description. All patients were part of an ongoing single-center prospective research cohort study (between 1999 and 2015) of advanced neuroimaging in CAA survivors.^{15–17} Patients were included in our study if they met the following criteria: (1) probable CAA according to the Boston criteria¹⁸ and (2) the availability of at least 2 MRI sessions including a DWI sequence. To avoid possible effects of acute ICH, all scans performed within 2 weeks of a prior ICH were excluded. Demographic information, prior ICH or ischemic stroke, *APOE* genotype, and cardiovascular risk factors (e.g., hypertension, diabetes mellitus, atrial fibrillation) were collected at time of cohort entry.

Standard protocol approvals, registrations, and patient consents. The study protocol was approved by the local institutional review board, and informed consent was obtained from each participant.

Neuroimaging acquisition. All patients underwent 1.5T MRI as previously described.^{17,19} Because of the clinical nature of this cohort, there was unavoidable heterogeneity in the imaging protocols. Imaging sessions included a combination of the following sequences: DWI and apparent diffusion coefficient (ADC), fluid-attenuated inversion recovery (FLAIR), T1-weighted, and blood-sensitive sequences (e.g., T2* gradient-recalled echo [GRE] or susceptibility-weighted imaging [SWI]).

Assessment of DWI lesions. DWI lesions were assessed by a board-certified neuroradiologist (M.W.V.) on all available time points. A lesion was considered a DWI lesion if it appeared hyperintense on DWI and hypointense or isointense on ADC. We previously reported high interrater reliability for assessing DWI lesions in these patients.⁶ Lesions were excluded if they appeared on initial MRI as hypointense on blood-sensitive scans (e.g., T2* GRE or SWI), as this would reflect susceptibility artefact caused by a CMB ($n = 1$). The size of each DWI lesion was assessed by manually outlining the DWI lesion on a single slice at the level of the lesion's greatest diameter, in MRIcron (version 2015). The number of voxels occupied by the outlined area, provided by MRIcron, was used as lesion size. The appearance of DWI lesions on follow-up imaging was assessed by 2 experienced raters in consensus (S.J.v.V. and A.L.). They noted appearance of the lesion on the corresponding location on available FLAIR, T1, and blood-sensitive sequences.

Assessment of other neuroimaging markers. Other markers of cerebral small vessel disease were assessed cross-sectionally in each individual at a single MRI time point, blinded to presence of DWI lesions, as follows.

Chronic cortical CMIs were assessed by 2 raters (S.J.v.V. and N.B.) on FLAIR and T1-weighted images in MeVisLab (MeVis Medical Solutions AG, Bremen, Germany), according to recently proposed guidelines.^{13,20} Chronic cortical CMIs were only assessed in patients who had at least a 3D T1-weighted image (with

a resolution of $1 \times 1 \times 1 \text{ mm}^3$) and either 2D or 3D FLAIR at any time point. A chronic cortical CMI was considered if the lesion appeared hypointense on T1, hyperintense on FLAIR, and isointense on blood-sensitive sequences. The lesion had to be restricted to the cortex, distinct from perivascular spaces, and $\leq 4 \text{ mm}$ in longest diameter. Interrater agreement as assessed by the intraclass correlation coefficient (ICC) was good (ICC = 0.80). All possible chronic cortical CMIs were evaluated in a consensus meeting by 2 raters (S.J.v.V. and L.X.) to determine definite ratings.

Number of CMBs and presence of cortical superficial siderosis was identified for each patient on blood-sensitive scans at the first available MRI time point according to previously published guidelines.^{3,21} WMH volume was assessed semiautomatically, with an intensity-based threshold algorithm, on FLAIR scans at the first available MRI time point ($n = 48$), or any time point thereafter ($n = 24$), as described previously.²² WMH volume was expressed as a percentage of total intracranial volume, as calculated by the fully automated software suite FreeSurfer (version 5.3.0), using the ICH-free hemisphere.^{23,24} Total brain volume was assessed on the same MRI scans as WMH volume, expressed as the sum of gray matter volume, white matter volume, and intraventricular CSF, as calculated by FreeSurfer.

Statistical analysis. To determine risk factors for the occurrence of DWI lesions, we performed χ^2 tests or independent samples t tests where appropriate. For the association between DWI lesions and other neuroimaging markers as well as cognition, we performed χ^2 tests, independent samples t tests, or a Mann-Whitney U test for nonparametric data. To adjust for potential confounders, we performed binary logistic regression analysis. The association between lesion size and visibility at follow-up was assessed with an independent samples t test.

RESULTS General findings. In total, 79 patients with probable CAA (mean age 68.9 ± 7.8 years; 19 male [24%]) were included in this study (figure e-1 at [Neurology.org](#)), 51 with a history of symptomatic lobar ICH. A total of 221 DWI scans were assessed for DWI lesions. As per inclusion criteria, all 79 patients had at least 2 available DWI scans (40 patients had 3, 21 had 4, and 2 had 5). The mean time interval between scans was 10.5 months (range 0.4–80.3). A total of 28 of 79 (35%) patients had 1 or more DWI lesions at any MRI time point. A total of 21 of 79 patients (27%) had 1 or more DWI lesions at a single time point, and 7 of 79 patients (9%) at more than 1 time point. In total, 60 DWI lesions were found in this dataset, 38 of which were located in the white matter, 16 in the cortical gray matter, and 6 in the cerebellum (figures 1 and 2).

Risk factors for DWI lesions. Patients with 1 or more DWI lesions at the first MRI time point ($n = 14$; 18%) were not more likely to have an additional DWI lesion on follow-up compared to patients without a DWI lesion at their first MRI time point ($n = 65$); 2 out of these 14 patients (14%) had a DWI lesion on the second MRI scan, compared to 9 out of 65 patients (14%) without a prior DWI lesion (χ^2 test; $p = 0.966$). Moreover, patients with DWI

Figure 1 Diffusion-weighted imaging (DWI) lesions are associated with chronic cortical cerebral microinfarcts (CMIs)

(A) A DWI lesion in the white matter, detected at the second MRI time point. (B) Two chronic cortical CMIs were identified on fluid-attenuated inversion recovery (FLAIR) and T1 in the same patient at the first MRI time point, one of which is shown here.

lesions (one or more at any MRI time point; $n = 28$) did not differ in age, sex, or vascular risk factors compared to patients without DWI lesions ($n = 51$) (table 1). Repeating the analyses for patients with

Figure 2 Evolution of diffusion-weighted imaging (DWI) lesions

(A) Two DWI lesions in the white matter. (B) Follow-up imaging 2 years later shows 2 cavitated lesions at the same location on fluid-attenuated inversion recovery (FLAIR). (C) No T1-weighted MRI scan was available at this time point. Another case of a DWI lesion in the white matter in a different patient. (D) Follow-up imaging 1 year later shows a hyperintense lesion at the same location on FLAIR, without cavitation. The lesion appears hypointense on T1 (inset) (although less hypointense compared to the lacunar infarct located above it).

DWI lesions at 1 time point ($n = 21$) compared to more time points ($n = 7$) did not alter the results.

Association with other neuroimaging markers and cognition. Presence of chronic cortical CMIs could be assessed in 68 patients, and were found in 25 (37%). Patients with DWI lesions (one or more at any MRI time point; $n = 28$) were more likely to have chronic cortical CMIs compared to patients without any DWI lesions (χ^2 test; $p = 0.001$) (figure 1). Moreover, patients with DWI lesions more often had cortical superficial siderosis compared to patients without any DWI lesions ($p = 0.010$). These associations remained statistically significant after adjusting for age at first MRI and sex. We found no statistically significant associations between the presence of DWI lesions and the presence of other neuroimaging markers of small vessel disease, although a positive trend was observed for CMB number (table 2). Repeating the analyses for patients with DWI lesions at 1 time point ($n = 21$) compared to more time points ($n = 7$) did not alter the results. Finally, patients with cortical DWI lesions did not more often have chronic cortical CMIs (7/11) compared to patients with DWI lesions in other locations (9/17; χ^2 test; $p = 0.851$).

We explored the relation between DWI lesions and cognition. A total of 48 patients underwent a Mini-Mental State Examination (MMSE) within 3 months of the first MRI time point. Mean MMSE was not different between patients with 1 or more DWI lesions at any MRI time point (27.5 ± 2.8) compared to patients without DWI lesions (27.8 ± 2.4).

DWI lesion evolution. For 39/60 DWI lesions, >1 imaging sequence was available at follow-up to determine lesion evolution (time interval 9.5 months [range 0.4–58.1]). A total of 24 of 39 DWI lesions (62%) were still visible as signal abnormalities on other sequences (T1, FLAIR) on follow-up MRI. The mean interval between scans did not differ for lesions that were visible on follow-up (9.5 months [range 2.6–51.8]), compared to lesions that were not visible on follow-up (9.6 months [range 0.4–58.1]). Of the DWI lesions that were visible as signal abnormalities on follow-up MRI, 16 were located in the white matter, 6 in the cortical gray matter, and 2 in the cerebellum. In terms of their appearance, 5 were demarcated as cavitated infarcts (of which 4 were located in white matter) (figure 2, A and B) on follow-up. Another 18 lesions were visible as a signal abnormality on T1 or FLAIR sequences, but appeared noncavitated (figure 2, C and D) (10 were hyperintense on FLAIR and hypointense on T1; 6 were hyperintense on FLAIR and isointense on T1; 2 were hypointense on T1 but had no FLAIR available to assess). One DWI lesion showed evidence of

Table 1 Risk factors for diffusion-weighted imaging (DWI) lesions

	Patients with 1 or more DWI lesions (n = 28)	Patients with no DWI lesions (n = 51)	p Value
Age, y	69.7 ± 8.1	68.5 ± 7.7	0.517
Male	6 (21)	13 (25)	0.686
Hypertension	18 (64)	27 (53)	0.330
Antihypertensive medication	16 (57)	30 (59)	0.806
Diabetes mellitus	3 (11)	3 (6)	0.438
Smoking (ever)	13 (46)	19 (37)	0.427
Hyperlipidemia	13 (46)	21 (41)	0.652
Lipid-lowering medication	10 (36)	16 (31)	0.739
Atrial fibrillation	3 (11)	6 (12)	0.888
APOE ε4 status ^a	11 (50)	21 (47)	0.798

Data are presented as mean ± SD or n (%).

^aAPOE ε4 1 or 2 alleles; data were available for 67 patients.

hemosiderin deposition on follow-up, compatible with hemorrhagic transformation (figure 3).

DWI lesions that were visible on other sequences (T1, FLAIR) at follow-up tended to be larger at initial presentation (14.9 ± 13.5 voxels) compared to DWI lesions that were not visible on follow-up (7.9 ± 3.4 voxels) ($p = 0.058$).

DISCUSSION In this study, we assessed presence, determinants, and the longitudinal aspect of DWI lesions in a cohort of patients with probable CAA who underwent multiple imaging sessions. We found that

DWI lesions occurred frequently in a broad cross-section of patients with CAA. They were strongly associated with presence of chronic cortical CMIs and cortical superficial siderosis. More than 60% of the observed DWI lesions evolved into chronic brain lesions, and the minority showed cavitation.

DWI lesions have been found in 28%–41% of patients with acute ICH.^{4,5,25–27} Even outside the time window of acute ICH, DWI lesions are present in ~15% of patients with CAA.^{4,6} These numbers suggest that DWI lesions are frequent findings in patients with CAA, especially when compared to the low prevalence of <1% as reported for the general population.^{28,29} In the present study, we found a point prevalence of 18% at the first MRI time point, which is similar to previous observations in patients with CAA outside the time window of acute ICH.^{4,6} Interestingly, when considering all MRI time points, we observed an even higher overall prevalence of 35%. This further underlines that DWI lesions are indeed very frequent, and as previously suggested detecting even a single DWI lesion could indicate an annual incidence of tens to even hundreds of new lesions in an individual patient.^{9,30} This is in line with estimations of the total burden of CMIs at autopsy,^{11,31} further supporting the conclusion that DWI lesions represent acute microinfarction.

In that context, a major strength of this study is that we were able to assess chronic cortical CMIs for the first time, to our knowledge, on clinical MRI scans in patients with CAA and to assess the association with DWI lesions. Chronic cortical CMIs have recently emerged as a novel imaging marker in the context of cerebral small vessel disease, and were first described in ex vivo MRI histopathology studies performed at 7T MRI,^{12,32,33} and later also on high-resolution in vivo 3T MRI scans.^{13,34–36} Despite the lack of high-resolution research scans in our current study, we could still identify chronic cortical CMIs in 37% of patients, suggesting that CMIs are frequent lesions in the context of CAA, consistent with neuropathologic observations.^{11,37,38} The prevalence of 37% appears high relative to recently reported prevalences of CMIs identified on 3T MRI in patients with stroke or TIA (15%),³⁵ patients attending a memory clinic (32%),¹³ or the general population (6%).³⁶ As hypothesized, DWI lesions were associated with the presence of chronic cortical CMIs. This novel finding suggests that DWI lesions and chronic cortical CMIs share similar underlying pathophysiologic mechanisms, and that the nature of DWI lesions in patients with CAA might be primarily ischemic—most likely representing acute microinfarction—in most cases. Of note, it has been previously suggested that hemorrhagic mechanisms are also into play creating DWI lesions in CAA or ICH patients.¹⁰

Table 2 Associations between diffusion-weighted imaging (DWI) lesions and other neuroimaging markers

	Patients with 1 or more DWI lesions (n = 28)	Patients with no DWI lesions (n = 51)	p Value
Presence of chronic cortical CMIs ^a	16 (62)	9 (18)	0.001
Intracerebral hemorrhage (ever)	20 (71)	31 (61)	0.344
Recurrent hemorrhages	7 (25)	9 (18)	0.437
Ischemic stroke ^b	1 (4)	4 (8)	0.465
Normalized WMH volume ^c	1.97 ± 0.99	1.92 ± 1.12	0.822
Brain volume ^d	926 ± 88	927 ± 90	0.964
Microbleed number ^e	44.0 (0–585)	14.5 (0–442)	0.117
Presence of cortical superficial siderosis ^f	19 (71)	19 (37)	0.010

Abbreviations: CMIs = cerebral microinfarcts; WMH = white matter hyperintensities.

Data are presented as n (%), mean ± SD, or median (range).

^aData were available for 68 patients.

^bData were available for 77 patients.

^cWMH volume is presented as a percentage of total intracranial volume; data were available for 72 patients.

^dBrain volume represents the sum of gray matter volume, white matter volume, and CSF (in mL); data were available for 72 patients.

^eData were available for 66 patients.

^fData were available for 75 patients.

Figure 3 Hemorrhagic transformation of a diffusion-weighted imaging (DWI) lesion

(A) A cortical DWI lesion. (B) Follow-up imaging 4.3 years later shows no signal abnormalities at the same location on fluid-attenuated inversion recovery (FLAIR), but a hypointense lesion on susceptibility-weighted imaging (SWI) (C), suggesting this DWI lesion underwent hemorrhagic transformation.

However, only 1 incident DWI lesion underwent hemorrhagic transformation in our cohort (figure 3). The association of DWI lesions with cortical superficial siderosis is intriguing and somewhat unexpected, as siderosis reflects a hemorrhagic rather than ischemic event. Cortical superficial siderosis has emerged as a key neuroimaging marker of CAA, consistently associated with high risk of future ICH and transient focal neurologic episodes. Although the exact mechanisms are under investigation, cortical superficial siderosis is hypothesized to reflect bleeding into the subarachnoid space or subpial cortical layers from severely affected amyloid-laden leptomeningeal arteries.²¹ Hence, siderosis on MRI may be considered a marker of more severe or focally active underlying disease, which could explain the significant association with DWI lesions. Interestingly, others have suggested that siderosis pathologically may be linked to ischemic tissue injury locally.³⁹ Clearly, the relation between siderosis and DWI lesions warrants further investigation.

More than half of the DWI lesions evolved into chronic lesions that were visible as signal abnormalities on FLAIR or T1 on follow-up imaging, and only a minority showed cavitation. A previous study reported on the appearance of DWI lesions at follow-up imaging (7.1 ± 4.7 months later), and similarly found that 5/9 lesions could indeed be identified as T1 hypointensities with or without a hyperintense signal on FLAIR.¹⁴ Another recent study showed that 12/25 DWI lesions detected within 2 weeks after ICH were still visible on T2 and FLAIR at follow-up imaging 3 months later.⁴⁰ Although this study included mainly patients with deep ICH, their observations of the fate of DWI lesions are very much in line with ours. It is not clear what exactly determines whether a DWI lesion will evolve into a chronic

lesion on structural MRI. Interestingly, the acute lesions that turned into a chronic lesion in our study tended to be larger at initial presentation and located in the subcortical white matter.

Three modalities have been described for the detection of CMIs: autopsy, high-resolution structural MRI, and DWI. However, none of these detection methods is capable of capturing the whole CMI burden, as each of these modalities present with their own limitations. Postmortem examination of the brain at autopsy offers the highest resolution to detect the smallest CMIs under the microscope. However, only a fraction of the brain is examined (usually $<0.01\%$) as only a few samples are taken at routine autopsy. Hence, detecting even 1 or 2 CMIs under the microscope suggests a total burden of hundreds to thousands of CMIs throughout the brain.³¹ Due to their numerous and widespread appearance, CMIs are believed to be capable of substantially disrupting brain structure and function, and hence likely to affect cognition during life.¹¹ The recent advancement of high-field strength *in vivo* structural MRI offered the opportunity to appreciate chronic CMIs in living individuals for the first time.¹² Chronic CMI detection has been restricted to the cortical gray matter, as CMIs are not readily distinguishable from WMH or perivascular spaces in the white matter.³² In that context, DWI provides true whole brain coverage for the detection of CMIs, albeit limited by the small time window of capturing CMIs that are only visible on DWI in the acute or subacute state, for up to 2 weeks.^{7,8} Hence, combining high-resolution structural MRI with DWI offers the opportunity to appreciate a wider spectrum of total CMI burden *in vivo*. In addition, our study provides preliminary evidence that a proportion of small acute DWI lesions lead to measurable brain parenchymal damage at follow-up imaging, thus warranting further investigation as predictors of large scale alterations and clinical deterioration.³⁰

A major limitation of this study is the relatively small number of patients, which limited more in-depth statistical analyses, including the relation with cognition, an important topic for future studies. We purposefully only included patients with at least 2 DWI scans, and excluded all scans that were made within the acute time window of the ICH. As such, the patients who were entered into the analysis represent a selected sample of patients with CAA from the original cohort. Moreover, the relatively small sample size did not allow us to take into account some of the heterogeneity of the dataset (e.g., scan protocols of varying quality, varying intervals between MRI scans) as well as potential other factors that may have affected DWI lesion appearance (e.g., treatment, hypertension). Finally, imaging was performed in a clinical setting, which raises the possible concern

of an overestimation of DWI incidence. Despite these limitations, our study is novel and hypothesis-generating, awaiting replication in larger (preferably prospective) studies, and validation by means of ex vivo MRI histopathology studies of DWI lesions.

DWI lesions are common neuroimaging findings in patients with probable CAA. More than 60% of the observed DWI lesions evolve into chronic lesions, and the minority shows cavitation. Only 1 lesion underwent hemorrhagic transformation. The neuroimaging signature as well as their association with chronic cortical CMIs and their occurrence in a broad cross-section of patients strongly suggest that DWI lesions in individuals with CAA have an ischemic etiology, and in fact represent part of the CMI spectrum.

AUTHOR CONTRIBUTIONS

M.W.V., S.M.G., and S.J.v.V. designed the study. M.W.V., M.E.G., P.F., G.B., L.X., N.B., A.C., A.L., and S.J.v.V. were involved in data acquisition and/or analysis of the data. A.A. managed the database. S.J.v.V. performed statistical analysis and wrote the first draft of the manuscript. All authors critically read the manuscript, provided feedback, and approved submission of the manuscript.

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DISCLOSURE

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