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## Staging cerebral amyloid angiopathy: from marker to model

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A watercolor illustration of a brain, showing the intricate branching patterns of the cerebral cortex. The brain is rendered in warm tones of orange, yellow, and red, with dark blue and black spots representing amyloid plaques and hemorrhages. The background is a soft, light yellow. A large, dark blue number '6' is centered on the page.

# 6

STRIPED OCCIPITAL CORTEX AND INTRAGYRAL  
HEMORRHAGE: NOVEL MRI MARKERS FOR  
CEREBRAL AMYLOID ANGIOPATHY

# Chapter 6 | Striped occipital cortex and intragyral hemorrhage: novel MRI markers for Cerebral Amyloid Angiopathy

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## Abstract

**Background and aim:** To investigate whether a striped occipital cortex and intragyral hemorrhage, two markers recently detected on ultra-high-field 7T-MRI in hereditary CAA, also occur in sporadic CAA (sCAA) or non-sCAA intracerebral hemorrhage (ICH).

**Methods:** We performed 7T-MRI in patients with probable sCAA and patients with non-sCAA-ICH. Striped occipital cortex (linear hypointense stripes perpendicular to the cortex) and intragyral hemorrhage (hemorrhage restricted to the juxtacortical white matter of one gyrus) were scored on  $T_2^*$ -weighted MRI. We assessed the association between the markers, other CAA-MRI markers and clinical features.

**Results:** We included 33 patients with sCAA (median age 70 years) and 29 patients with non-sCAA-ICH (median age 58 years). Striped occipital cortex was detected in one (3%) patient with severe sCAA. Five intragyral hemorrhages were found in four (12%) sCAA patients. The markers were absent in the non-sCAA-ICH group. Patients with intragyral hemorrhages had more lobar ICHs (median count 6.5 versus 1.0), lobar microbleeds (median count >50 versus 15), and lower median cognitive scores (MMSE: 20 versus 28, MOCA: 18 versus 24) compared with patients with sCAA without intragyral hemorrhage. In 12 (36%) patients sCAA diagnosis was changed to mixed-type small vessel disease due to deep bleeds previously unobserved on lower-field-MRI.

**Conclusion:** Whereas a striped occipital cortex is rare in sCAA, 12% of patients with sCAA have intragyral hemorrhages. Intragyral hemorrhages seem to be related to advanced disease and their absence in patients with non-sCAA-ICH could suggest specificity for CAA.

**Data access statement:** Information about the dataset is available on request.



## Introduction

Sporadic Cerebral Amyloid Angiopathy (sCAA) is a frequent cause of intracerebral hemorrhage (ICH) in the elderly, characterized by the deposition of the protein amyloid- $\beta$  in the cerebrovasculature.<sup>1</sup> The Boston criteria enable clinicians to diagnose possible or probable CAA during life based on clinical symptoms and imaging markers.<sup>2</sup> Since the development of the criteria, new CAA-related MRI markers have improved their sensitivity and specificity.<sup>2</sup>

Recently we detected two novel MRI markers on 7-tesla (7T) MRI in patients with Hereditary Dutch-type CAA (D-CAA), an hereditary form of CAA: a pattern of the occipital cortex and intragyral hemorrhages.<sup>3</sup> A striped occipital cortex, defined as a pattern of separate, hypointense linear stripes at  $T_2^*$ -weighted MRI perpendicular to the pial surface of the cortex, occurred in 40% of patients with symptomatic D-CAA. Intragyral hemorrhage, defined as parenchymal hemorrhage restricted to the juxtacortical white matter of an individual gyrus, occurred in 47% of patients with symptomatic D-CAA.<sup>3</sup> The prevalence of these markers in sCAA and their specificity for CAA pathology is yet unknown.

## Aims

Our aim was to investigate the prevalence and specificity of the striped occipital cortex and intragyral hemorrhages in patients with sCAA and in patients with non-sCAA related ICH and to assess their association with clinical features and CAA-related MRI markers.

## Methods

### *Study participants*

We included patients diagnosed with sCAA who participated in our ongoing studies on sCAA disease progression: FOCAS (Follow-up in sporadic Cerebral Amyloid angiopathy Study) and STRIP (The striped occipital cortex sign, a new MRI marker for sporadic cerebral amyloid angiopathy). We included patients with non-sCAA related ICH from the FETCH (Finding the ETiology in spontaneous Cerebral Hemorrhage) study, a collaborative study between the University Medical Centers of Utrecht, Nijmegen and Leiden. Details on the inclusion process of the studies can be found in the supplementary methods.

For all participants data on demographics, medical history (hypertension, diabetes mellitus, hypercholesterolemia) and clinical symptoms (symptomatic ICH and cognition) were obtained by questionnaires. All patients with sCAA underwent cognitive screening in the form of a Mini Mental State Exam (MMSE) and Montreal Cognitive Assessment (MOCA).<sup>4,5</sup> The ethics committees of the University Medical Centers of Leiden, Utrecht and Nijmegen approved the studies. Written informed consent was obtained from all participants.



## *MRI*

Details on image acquisition and scan parameters can be found in the supplementary methods.

### *Image analysis*

We scored the striped occipital cortex and intragyral hemorrhages as previously described by our group on  $T_2^*$ -weighted images: the striped occipital cortex was defined as linear hypointense stripes perpendicular to the pial surface of the cortex, intragyral hemorrhage was defined as an hemorrhage restricted to the juxtacortical white matter of the brain following the contours of the cortical grey matter and was scored according to number and location. The following MRI markers associated with small vessel disease (SVD) were scored according to the Standards for Reporting Vascular changes on neuroimaging (STRIVE) criteria: microbleeds, macrobleeds, cortical superficial siderosis (cSS), white matter hyperintensities and enlarged perivascular spaces in the centrum semiovale (CSO-EPVS).<sup>6</sup> Two independent observers (E.A.K. and S.V.) scored the two novel MRI markers. The other markers were scored by one observer (E.A.K). Because the observers had to review the MRI scans for the study they could not be blinded for ICH location or CAA status. However, both observers were blinded for the demographics, medical history and clinical symptoms of the participants. Non-concordant findings were discussed with a third observer with >15 years of experience in the field (M.A.A.v.W.) to obtain consensus. Definitions of the markers can be found in the supplementary methods.

### *Data analysis*

Descriptive statistics were performed for baseline characteristics. For both novel MRI markers the interobserver variation (kappa) and the grading of interobserver agreement was assessed.<sup>7</sup> We calculated the proportion of patients with sCAA (all

and in patients with sCAA patients and previous symptomatic ICH) and patients with non-sCAA ICH with a striped occipital cortex and/or intragyral hemorrhages, as well as the difference between these proportions including 95% confidence intervals (95% CI) with continuity correction. We calculated proportions and medians of MRI markers and cognitive scores in patients with sCAA and compared these in patients with sCAA with and without intragyral hemorrhages. Because our study was exploratory and the number of participants with the novel markers was expected to be relatively low, we decided not to calculate formal p-values but to perform only descriptive statistics for the association between the markers and the MRI and cognitive outcomes.

## Results

We included 33 patients with probable sCAA and 29 patients with non-sCAA ICH. The median age of the 33 patients with sCAA was 70 years (range 55-83), 13 (39%) were women and 19 (58%) had a history of symptomatic lobar ICH. The median age of the 29 patients with non-sCAA ICH was 58 years (range 18-84) and 7 (24%) of them were women. Of the 29 non-sCAA ICH participants 23 (79%) had a deep and 6 (21%) an infratentorial ICH (Table 1).

**Table 1:** Clinical characteristics and presence of the novel MRI markers.

	sCAA (n=33)	Non-sCAA ICH (n=29)
Median age in years (range)	70 (55-83)	58 (18-84)
Women (%)	13 (39)	7 (24)
Symptomatic ICH (%)	19 (58)	29 (100)
Lobar (%)	19 (58)	0 (0)
Deep (%)	0	23 (79)
Infratentorial (%)*	0	6 (21)
Hypertension (%)	16 (49) <sup>†</sup>	19 (67)
Hypercholesterolemia (%)	9 (27) <sup>†</sup>	8 (28)
Diabetes Mellitus type 2 (%)	1 (3) <sup>†</sup>	0
<i>Novel markers</i>		
Striped occipital cortex on MRI (%)	1 (3)	0
Intragyrally hemorrhage on MRI (%)	4 (12)	0

\*ICH located in the cerebellum or brainstem.

<sup>†</sup>n=32, information was not available for one CAA participant.



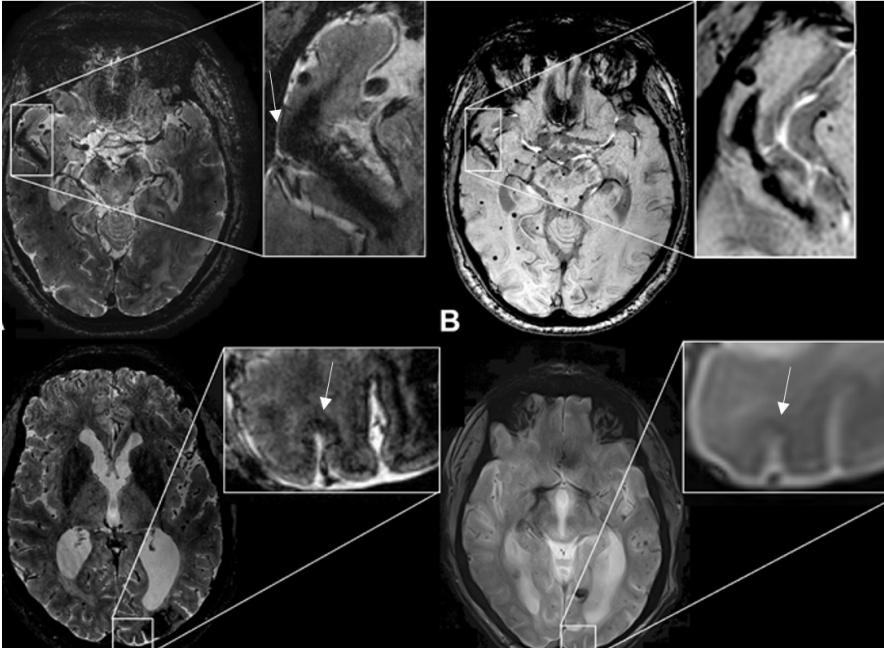


We found a striped occipital cortex in one sCAA patient (3%) and in none of the patients with non-sCAA ICH (difference in proportions 0.03, 95% CI -0.12 to 0.18). We found five intragyral hemorrhages in four patients with sCAA (12%) and none of the patients with non-sCAA ICH and intragyral hemorrhage (difference in proportions 0.12, 95% CI -0.05 to 0.29). If we looked at the presence of the novel markers in patients with sCAA and previous symptomatic ICH only, we found that 1 out of 19 (5%) had a striped occipital cortex compared to none of the patients with non-sCAA ICH (difference in proportions 0.05, 95% CI -0.10 to 0.28), and 4/19 (21%) of patients with sCAA and previous symptomatic ICH had intragyral hemorrhages compared to none of the patients with non-sCAA ICH (difference in proportions 0.21, 95% CI 0.01 to 0.46). The interobserver variation (Kappa statistic) for striped occipital cortex was perfect (1.00) and for intragyral hemorrhage almost perfect (0.90).

We compared the patients with sCAA and the novel MRI markers to the patients with sCAA without. The participant with the striped occipital cortex was 64 years old and had an advanced stage of sCAA; he had 8 lobar ICH on MRI of which at least 1 had been documented to be symptomatic, over 50 lobar MB and focal cSS. Clinically he had vascular dementia with a MOCA score of 13/25 (MMSE score was not available for this participant). The characteristics of the patients with sCAA and intragyral hemorrhage and the patients with sCAA without intragyral hemorrhage are shown in Table 2. Two participants with intragyral hemorrhage had EPVS visible in the same gyrus as the intragyral hemorrhage (Figure 2).

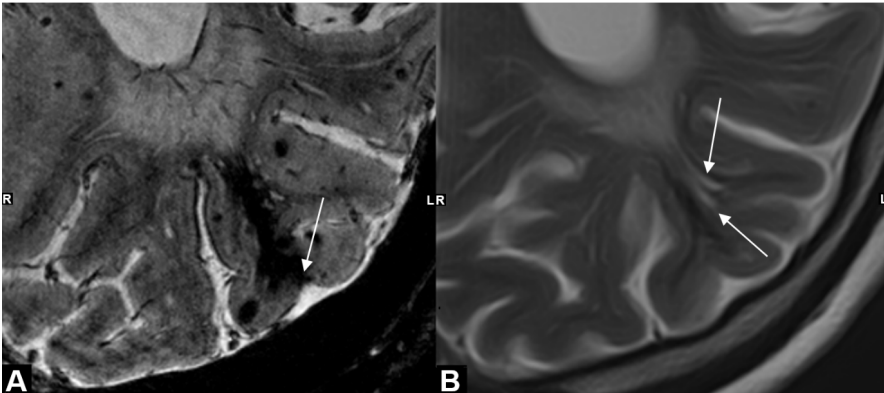
Two of the intragyral hemorrhages were located in the temporal lobe and three in the occipital lobe. The participant with the striped occipital cortex had an occipitally located intragyral hemorrhage. When examining the intragyral hemorrhages closely, we noticed that the susceptibility artifact on  $T_2^*$ -weighted MRIs – although largely confined to the juxtacortical white matter – also showed some extension in the overlying cortex. This cortical involvement was always of limited size, but was present in all intragyral hemorrhages (Figure 1B). Three of the four patients with intragyral hemorrhages also underwent 3T-MRI on the same day. We screened the corresponding susceptibility-weighted 3T-MRI scans and were able to distinguish the intragyral hemorrhages retrospectively in all three patients (Figure 1C). The patient with a striped occipital cortex and an intragyral hemorrhage had a  $T_2^*$ -weighted 3T-MRI of the brain six months after the 7T-MRI was performed. We were not able to distinguish the characteristic features of a striped occipital cortex at 3T, although we did see an intracortical hypointense signal at the location of the striped occipital cortex (Figure 1D).

Figure 1: Intragyral hemorrhage and striped occipital cortex on 7T- and 3T-MRI.



MRI scans of a patient with sCAA showing: A. Intragyral hemorrhage on  $T_2^*$ -weighted 7T-MRI, showing cortical involvement (arrow) B. the same intragyral hemorrhage on susceptibility weighted (SWI) 3T-MRI, C. striped occipital cortex on  $T_2^*$ -weighted 7T-MRI (arrow) and D. on SWI 3T-MRI (arrow).

Figure 2: Example of characteristic shape of intragyral hemorrhage and extended perivascular spaces.



MRI scans of a patient with sCAA showing: A. Intragyral hemorrhage on  $T_2^*$ -weighted 7T-MRI with cortical involvement (white arrow) and B. presence of enlarged perivascular spaces (EPVS) (white arrows) in the same gyrus as the intragyral hemorrhage on  $T_2$ -weighted 3T-MRI; note the similar shape of the EPVS and the susceptibility artefact of the intragyral hemorrhage on  $T_2$ -weighted MRI, possibly suggesting that intragyral hemorrhage is caused by blood leakage from a cortical microbleed into an EPVS.

**Table 2:** Characteristics of sCAA patients with intragyral hemorrhage compared to sCAA patients without.

	sCAA with intragyral hemorrhage (n=4)	sCAA without intragyral hemorrhage (n=29)
Median age in years (range)	64.5 (62-71)	71 (55-83)
Symptomatic ICH (%)	4 (100)	15 (52)
Median number of symptomatic lobar ICH (range)	1.5 (1-2)	0.5 (0-2)
ICH on MRI (%)	4 (100)	17 (59)
Lobar ICH (%)	4 (100)	17 (59)
Deep ICH (%)	1 (25)	2 (7)
Median lobar ICH count (range)	6.5 (4-10)	1.0 (0-9)
Median deep ICH count (range)	0.0 (0-2)	0.0 (0-1)
Median lobar microbleed count (range)	>50 (42- >50)	15 (0- >50)
Median deep microbleed count (range)	9.5 (0-36)	0 (0-11)
Median Fazekas score periventricular (range)*	3 (2-3)	3 (1-3)
Median Fazekas score deep (range)*	3 (2-3)	2 (1-3)
Enlarged CSO-EPVS (%) <sup>†</sup>	3 (100)	12 (100)
11-20 CSO-EPVS (%)	0 (0)	2 (17)
21-40 CSO-EPVS (%)	0 (0)	2 (17)
>40 CSO-EPVS (%)	3 (100)	8 (67)
Median MMSE score (range) <sup>‡</sup>	20 (17-24)	28 (18-30)
Median MOCA score (range) <sup>§</sup>	18 (13-21)	24 (13-29)
cSS (%)	2 (50)	19 (66)
Focal (%)	1 (25)	2 (7)
Disseminated (%)	1 (25)	17 (59)
Median hemisphere score (range)	0.5 (0-4)	2.0 (0-4)

<sup>†</sup>Intragyral hemorrhage participants n=3, CAA participants without intragyral hemorrhage n=28, due to missing MRI sequences.

<sup>‡</sup>Intragyral hemorrhage participants n=3, CAA participants without intragyral hemorrhage n=12, due to missing MRI sequences.

<sup>§</sup>Intragyral hemorrhage participants n=3, CAA participants without intragyral hemorrhage n=27.

<sup>¶</sup>Intragyral hemorrhage participants n=3, CAA participants without intragyral hemorrhage n=28.

We found that in 12 (36%) of the patients with sCAA, including two of the patients with intragyral hemorrhages, the 7T-MRI showed signs of hypertensive SVD (Table 2 and Figure 1 of the supplementary results). One of the patients with intragyral hemorrhages had two deep ICHs on MRI as well as several deep MBs, the other had deep MBs, changing their diagnosis to a mixed form of CAA and hypertension related SVD. However, all 12 patients had more extensive CAA-related SVD than hypertensive SVD: 9 (75%) had a symptomatic lobar ICH, 7 (58%) had cSS, and all had multiple lobar microbleeds.



## Discussion

We found that two recently described new MRI markers, a striped occipital cortex and intragyral hemorrhage, also occur in sCAA although less frequently than in hereditary D-CAA and only in patients with previous symptomatic ICH. Neither marker was observed in patients with non-sCAA ICH.

A striped occipital cortex on 7T-MRI has been described previously in a small histopathological study from our group, which identified iron depositions and calcification of the penetrating arteries of the cerebral occipital cortex as the histopathological substrate of the striping in one patient with sCAA and two patients with D-CAA.<sup>8</sup> As both iron and calcium co-localize with amyloid- $\beta$  and represent an advanced stage of amyloid- $\beta$  accumulation resulting in calcified arterioles, a possible explanation for the presence of the stripes is that they are amyloid-filled arterioles penetrating the occipital cortex.<sup>9</sup> Unfortunately, the striped occipital cortex is only visible on high-field MRI, limiting its use in clinical practice, although some darkening of the cortex could be seen in retrospect on 3T-MRI (Figure 1).

The pathophysiology underlying intragyral hemorrhages is unclear. In CAA the cortical and leptomeningeal arterioles are predominantly affected and not the vessels in the white matter. Therefore, it is striking that intragyral hemorrhages would be restricted to the juxtacortical white matter. However, all intragyral hemorrhages in this study showed cortical involvement and, therefore, we speculate that intragyral hemorrhages may have their origin in a cortical (micro) hemorrhage from which blood leaks into an enlarged perivascular space in the juxtacortical white matter, subsequently creating the characteristic shape of an intragyral hemorrhage. By looking in retrospect at the seven intragyral hemorrhages originally described in patients with D-CAA we found that they, too, show cortical involvement.<sup>3</sup> Two patients with intragyral hemorrhages had EPVS in the same gyrus as the intragyral hemorrhage, and the shapes of the intragyral hemorrhages and EPVS seem to correspond (Figure 2). Future prospective follow-up studies are necessary to investigate presence of EPVS at the location of future intragyral hemorrhages, and to investigate their prognostic meaning in CAA.

To our surprise, we found that 36% of the patients previously diagnosed with probable CAA according to the modified Boston criteria based on 1.5 or 3T-MRI had deep hemorrhages on ultra-high field 7T-MRI. The explanation for this finding might be that diagnosis of CAA had been made several months prior, based on lower field strength MR images which have a lower sensitivity to hemorrhagic markers compared to 7T-MRI.<sup>10, 11</sup> The Boston criteria have not been validated for 7T-MRI. By using this type of high quality MRI scans in this study we might have unearthed deep bleeds

which could not be seen on lower field MRI, which might be reason to consider changing the diagnosis from 'pure' CAA to a mixed form of CAA and possibly hypertension related changes.<sup>12</sup> This finding supports recent theories that state that SVD is a spectrum with pure CAA (lobar) and non-CAA, often hypertension related (deep) cerebral disease on opposing ends.<sup>12-15</sup> Many patients with sCAA will have signs of non-CAA related SVD or will develop these changes over time, due to the age-related comorbidity of (hypertensive) arteriopathy, which might be undetected in studies using conventional MRI techniques. The findings in this study highlight the difficulty of diagnosing CAA with accuracy during life and the fact that pure CAA might be less common than previously thought. The patients with mixed pathology in our study still had predominantly CAA pathology. If we would exclude these patients from our analysis the proportion of striped occipital cortex would increase to 1/21 (5%), and the proportion of intragryal hemorrhages would decrease to 2/21 (10%).

A limitation of this study is the small number of included patients. In addition, patients with very severe clinical symptoms due to CAA who were not able to undergo 7T-MRI because of their clinical condition could not be included in this study. We did not have pathological material to confirm the diagnosis CAA, and observers could not be blinded to the initial diagnosis of either sCAA or non-CAA ICH which could have caused a bias. Furthermore, there were differences in the 7T scan protocols for the CAA participants (FOCAS and STRIP) and the non-sCAA ICH participants (FETCH) although both studies used the same type of MRI scanner. The In-plane resolution of the FETCH  $T_2^*$  weighted scans was 0.5x0.5 mm, versus 0.24x0.24 mm of the FOCAS and STRIP  $T_2^*$  weighted scans.. As a striped pattern of the occipital cortex can be very subtle it is possible that this pattern was missed in the non-CAA ICH group. The patients with non-sCAA were younger compared to the patients with sCAA and we did not have access to healthy, age matched controls. Our results suggest that the two markers could be specific for sCAA, however as they were only found in patients with sCAA and previous ICH the markers might be specific for the CAA-ICH phenotype. Therefore, replication of our findings is warranted in additional (preferably larger) cohorts of CAA patients with different phenotypes, in other amyloid related diseases such as Alzheimer's Disease and in age-matched healthy individuals

Diagnosing CAA during life remains difficult, especially in the early stage of the disease. Although the two new MRI markers are only seen in advanced disease stages, they could help diagnose CAA in cases of doubt. Further research is necessary to investigate the prognostic value of these two new MRI markers, to further investigate the specificity of the markers for sCAA and to assess their underlying pathophysiology.

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## Supplemental material

### *Supplemental methods*

#### *Study participants*

Participants of the FOCAS and STRIP study were recruited via the (outpatient) clinic of the Leiden University Medical Center (LUMC), the Netherlands. The diagnosis CAA was established by an experienced neurologist and neuroradiologist prior to enrollment in the study. Inclusion criteria for the present study were: 1. Age  $\geq$  55 years, 2. Probable CAA based on the modified Boston criteria diagnosed at 1.5T- or 3T-MRI, 3. Ability and willingness to provide written informed consent. Participants who were not able to undergo 7T-MRI were excluded. All participants of the STRIP study had a 7T MRI scan of the brain. Of the FOCAS participants, 19 of the 23 participants were able to participate in the 7T MRI study. Of these 19, only 18 scans could be used for this study; image quality of one scan was severely degraded because of movement artifacts and was therefore excluded from further analyses. Four out of 23 participants could not participate in the 7T MRI study due to MRI safety issues, claustrophobia or because of their clinical condition. Participants of the FETCH study were recruited via the clinics of the University Medical Centers of Utrecht, Nijmegen and Leiden. The FETCH study included patients with spontaneous ICH between October 2013 and January 1<sup>st</sup> 2019.<sup>1</sup> We included all FETCH participants who had a 7T MRI and who did not have signs of possible or probable CAA on MRI according to the modified Boston criteria. Of all the FETCH participants, 51/221 (23%) underwent a 7T MRI. Of these 51, 29 had no signs of CAA on MRI and could therefore be included in our study.

#### *Image acquisition*

For all participants MRI was performed on two separate whole body human 7T-MR-systems (Philips, Best, The Netherlands) using a quadrature transmit and 32-channel receive head coil (Nova Medical, Wilmington, MA, USA) in either Utrecht or Leiden, The Netherlands.

STRIP and FOCAS participants were scanned in Leiden using a 2D flow-compensated transverse  $T_2^*$ -weighed gradient echo scan (repetition time (TR)/echo time (TE) 1851/25 ms, flip angle 60°, slice thickness 1.0 mm with a 0.1 mm interslice gap, 92 slices and coverage of 10 cm, 240 x 180 x 100 mm field-of-view (FOV), 1000 x 751 matrix size – resulting in an in-plane spatial resolution of 0.24 x 0.24 mm, multiband factor 2), a 3D Fluid-Attenuated Inversion Recovery (FLAIR)

scan (TR/TE: 8000/328 ms, inversion time (TI): 2200 ms, 225 slices with no interslice gap, FOV 250 x 240 x 180 with a voxel size of 0.8 x 0.8 x 0.8 mm), and a 3D T<sub>1</sub>-weighted scan (TR/TE: 4.3/1.9 ms with a flip angle of 7 degrees, 193 slices with no interslice gap, a FOV of 246 x 246 x 174 with a voxel size of 0.9 x 0.9 x 0.9 mm). Participants of the FOCAS study underwent an extra scan, a 3D T<sub>2</sub>-weighted scan (TR/TE: 3400/305ms with a flip angle of 90 degrees, 543 slices with no interslice gap, FOV of 250x250x190 with a voxel size of 0.7x0.7x0.35). No T<sub>2</sub>-weighted scans were made for participants of the STRIP study.

FETCH participants were scanned using a dual echo 3D T<sub>2</sub>\*-weighted scan (TR/ first TE/ second TE: 20/6.9/15.8 ms; voxel size: 0.50 x 0.50 x 0.70 mm<sup>3</sup>) and 3D T<sub>2</sub> weighted images (TR/ TE): 3158/ 60 ms; voxel size: 0.70 x 0.70 x 0.70 mm<sup>3</sup>).

Participants in the FOCAS study also underwent a 3 Tesla (3T) MRI scan of the brain on the same day as the 7T-MRI scan, performed on a MRI scanner (Philips, Best, the Netherlands) using a standard 32-channel head coil. The participants were scanned using susceptibility weighted images (SWI) (TR/TE= 31/7.2ms, flip angle 17 degrees, 130 slices and an FOV of 230 x 190 x 130 mm with a voxel size of 0.6 x 0.6 x 1mm) and T<sub>2</sub>-weighted images (TR/ TE = 4744/80ms, flip angle 90 degrees, 48 slices with no interslice gap and an FOV of 220 x 176 x 144 mm with a voxel size of 0.5 x 0.6 x 3 mm). Some of the FETCH participants underwent 3T-MRI within weeks of the 7T-MRI scan. 3T-MRI in the FETCH was acquired by a standardized protocol including an axial T<sub>2</sub>\*-weighted sequence and FLAIR, both with 48 contiguous slices and 0.96 x 0.95 x 3.00mm<sup>3</sup> voxels, and a 3D T<sub>1</sub>-weighted sequence.

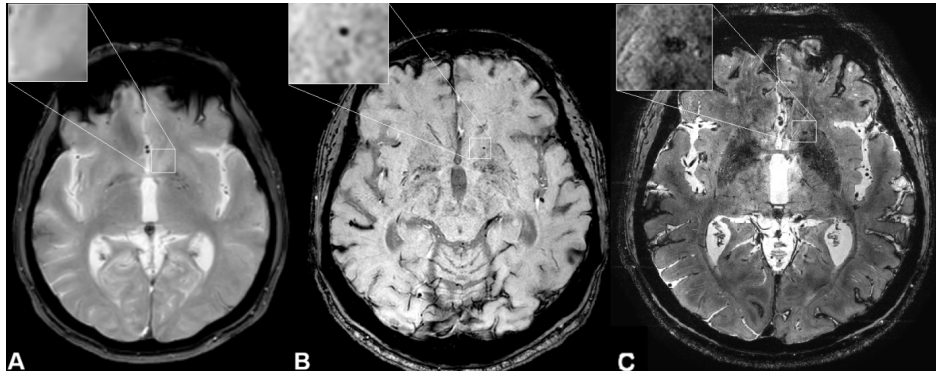
### *Image analysis*

Microbleeds (MB) were scored on T<sub>2</sub>\*-weighted scans according to the following locations: deep (including basal ganglia, thalamus, internal capsule, external capsule and deep white matter) and lobar (including frontal, parietal, temporal, occipital and insula).<sup>2</sup> MB were counted from 1-50, if participants had over 50 MB this was scored as >50. Cortical superficial siderosis (cSS) was scored on T<sub>2</sub>\*-weighted images according to location in the brain and categorized as focal, defined as cSS restricted to three or fewer sulci, or disseminated, defined as cSS affecting four or more sulci. In addition, cSS hemisphere score was calculated according to the method described previously.<sup>3</sup> <sup>4</sup> Number and location of ICH were scored on T<sub>2</sub>\*-weighted scans and 3D T<sub>1</sub>-weighted scans. Both periventricular and deep white matter hyperintensities were scored according to the Fazekas score on FLAIR images.<sup>5</sup> Enlarged perivascular spaces in the centrum semiovale (CSO-EPVS) were scored on 3D T<sub>2</sub>-weighted images according to the following categories; no EPVS, 1-10 EPVS, 11-20 EPVS, 21-40 EPVS, >40 EPVS.<sup>6</sup>



For the patients in whom the two new markers were detected at 7T-MRI we screened the corresponding 3T-MRI SWI scans acquired on the same day, when available, and any other previously made 3T-MRI scans, to see if we could retrospectively identify the markers at this conventional field strength as well.

Supplementary figure 1: A deep microbleed at 1.5T, 3T and 7T MRI.



MRI scan of a patient originally diagnosed with pure sCAA showing: A. The scan on which the original diagnosis was made, an 1.5T  $T_2^*$ -weighted scan, B. A higher quality 3T SWI scan, made three months after scan A, showing a previously unobserved microbleed in the caudate nucleus, C. A high field 7T  $T_2^*$ -weighted scan, made on the same day as scan B, showing a clearer image of the same microbleed in the caudate nucleus.

## Supplemental references

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