Supplementary 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 ≥ 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 1st 2019.[1] 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_1-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_2-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 07x07x0.35). No T_2-weighted scans were made for participants of the STRIP study.

FETCH participants were scanned using a dual echo 3D T_2*-weighted scan (TR/first TE/ second TE: 20/6.9/15.8 ms; voxel size: 0.50 x 0.50 x 0.70 mm3) and 3D T_2 weighted images (TR/ TE): 3158/ 60 ms; voxel size: 0.70 x 0.70 x 0.70 mm3).

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_2-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_2*-weighted sequence and FLAIR, both with 48 contiguous slices and 0.96 x 0.95 x 3.00mm^3 voxels, and a 3D T_1-weighted sequence.

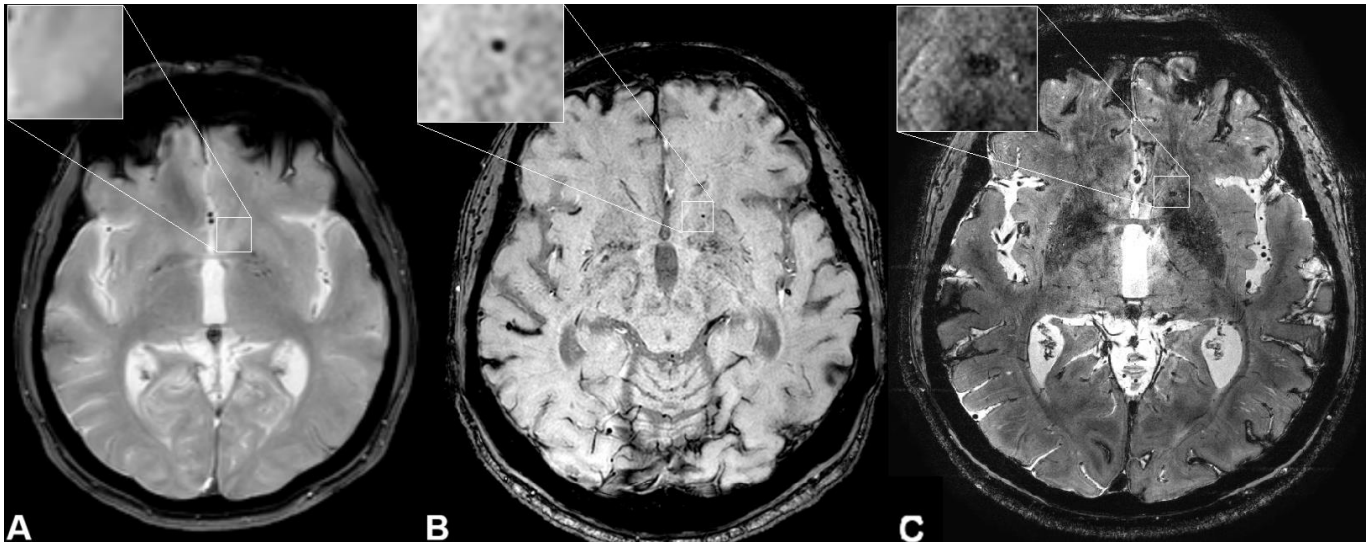
Image analysis

Microbleeds (MB) were scored on T_2*-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).[2] 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_2*-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.[3, 4] Number and location of ICH were scored on T_2*-weighted scans and 3D T_1-weighted scans. Both periventricular and deep white matter hyperintensities were scored according to the Fazekas score on FLAIR images.[5] Enlarged perivascular spaces in the centrum semiovale (CSO-EPVS) were scored on 3D T_2-weighted images according to the following categories; no EPVS, 1-10 EPVS, 11-20 EPVS, 21-40 EPVS, >40 EPVS.[6]

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 results

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

1. Jolink WM, Lindenholz A, van Etten ES, et al. Contrast leakage distant from the hematoma in patients with spontaneous ICH: A 7 T MRI study. *J Cereb Blood Flow Metab* 2020; 40: 1002-1011. 2019/05/31. DOI: 10.1177/0271678x19852876.
2. Gregoire SM, Chaudhary UJ, Brown MM, et al. The Microbleed Anatomical Rating Scale (MARS): reliability of a tool to map brain microbleeds. *Neurology* 2009; 73: 1759-1766. 2009/11/26. DOI: 10.1212/WNL.0b013e3181c34a7d.
3. Charidimou A, Linn J, Vernooij MW, et al. Cortical superficial siderosis: detection and clinical significance in cerebral amyloid angiopathy and related conditions. *Brain : a journal of neurology* 2015 2015/06/28. DOI: 10.1093/brain/awv162.
4. Charidimou A, Boulouis G, Roongpiboonsopit D, et al. Cortical superficial siderosis multifocality in cerebral amyloid angiopathy: A prospective study. *Neurology* 2017; 89: 2128-2135. 2017/10/27. DOI: 10.1212/wnl.0000000000004665.
5. Fazekas F, Chawluk JB, Alavi A, et al. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR American journal of roentgenology* 1987; 149: 351-356. 1987/08/01. DOI: 10.2214/ajr.149.2.351.
6. Potter GM, Chappell FM, Morris Z, et al. Cerebral perivascular spaces visible on magnetic resonance imaging: development of a qualitative rating scale and its observer reliability. *Cerebrovascular diseases (Basel, Switzerland)* 2015; 39: 224-231. 2015/04/01. DOI: 10.1159/000375153.
7. Koemans EA, van Etten ES, van Opstal AM, et al. Innovative Magnetic Resonance Imaging Markers of Hereditary Cerebral Amyloid Angiopathy at 7 Tesla. *Stroke* 2018; 49: 1518-1520. 2018/04/27. DOI: 10.1161/strokeaha.117.020302.