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AJNR Am J Neuroradiol published online 17 February 2025
http://www.ajnr.org/content/early/2025/02/17/ajnr.A8705

ORIGINAL RESEARCH

In vivo visualisation of Charcot-Bouchard Aneurysms on lenticulostriate arteries using 7T MRI

*Yeerfan Jiaerken, *Philip Benjamin, Christopher T. Rodgers, Lupei Cai, Stefania Nannoni, Andrew D MacKinnon, and Hugh S Markus
*Y.J. and P.B. contributed equally to this work

ABSTRACT

BACKGROUND AND PURPOSE: Charcot-Bouchard Aneurysms (CBA) are tiny aneurysms arising from small perforating arteries. Despite the potentially catastrophic consequences of rupture of these aneurysms, the existence and prevalence of CBAs is controversial. The literature in this area is sparse with most previous studies based on radiological case reports of single hemorrhage or histopathological analysis. 7T MRI provides higher spatial resolution than 3T MRI that enables imaging of the small perforating arteries. We determined whether CBAs could be detected in vivo using 7T MRI.

MATERIALS AND METHODS: 94 patients with ischemic stroke collected in the Cam-SVD prospective cohort were retrospectively included; 75 of them had lacunar infarcts due to presumed small vessel disease and 19 had non-lacunar infarcts due to presumed cardioembolism or large artery disease. Contrast enhanced 3D time-of-flight (TOF) angiography (MRA) and structural sequences were performed by 7T MRI. Two neuroradiologists independently reviewed the MR scans to identify aneurysms on the lenticulostriate arteries (LSA) bilaterally.

RESULTS: In 4 of the 94 subjects, CBAs were detected in the LSAs; of these three had a single CBA and one had two. The diameter of the parent vessel ranged from 0.26mm – 0.37mm, and the maximum diameter of the CBA ranged from 0.73mm – 1.39mm. Use of 3D images allowed differentiation of looped vessels, which could mimic aneurysms on 2D images, from true CBA.

CONCLUSIONS: We have demonstrated that 7T MRI can detect CBAs in vivo in humans. This technique could allow further longitudinal studies to determine the true prevalence and prognostic significance of CBAs.

ABBREVIATIONS: CBA: Charcot-Bouchard Aneurysms; LSA: lenticulostriate arteries; CamSVD: Cambridge 7T Cerebral Small Vessel Disease study; eGFR: estimated glomerular filtration rate; FA: flip angle

Received Nov 20, 2024; accepted after revision Feb 06, 2025.
From Stroke Research Group. Department of Clinical Neurosciences, (Y.J., L.C., S.N., H.S.M.) and Wolfson Brain Imaging Centre, Department of Clinical Neurosciences (C.T.R), University of Cambridge, UK. Department of Radiology, (Y.J.), Second Affiliated Hospital of Zhejiang University, School of Medicine, China. Department of Neuroradiology, Atkinson Morley Regional Neurosciences Centre, (P.B., A.D.M) St George's University Hospitals NHS Foundation Trust, UK.

Yeerfan Jiaerken was supported by the National Natural Science Foundation of China. (No. 82101984).
This study was funded by a project grant from the British Heart Foundation (PG/19/74/34670). Recruitment was supported by the National Institute for Health Research Clinical Research Network. Infrastructural support was provided by the Cambridge British Heart Foundation Centre of Research Excellence (RE/24/130011) and Cambridge University Hospitals NIHR Biomedical Research Centre (NIHR203312). The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS, or UK Department of Health and Social Care.

Corresponding author: Hugh S Markus, Stroke research group, R3, Box 83, Neurology Unit, Department of Clinical Neurosciences, University of Cambridge, Cambridge Biomedical Campus, Cambridge, CB2 0QQ. hsm32@medschl.cam.ac.uk

SUMMARY SECTION

PREVIOUS LITERATURE: Charcot-Bouchard Aneurysms (CBA) are tiny aneurysms (typically 0.05-2.5 mm in diameter) arising from small perforating arteries (typically < 0.3 mm in diameter), first described by Charcot and Bouchard in 1868. They are most commonly found in the distal lenticulostriate arteries (LSA) and postmortem studies have reported a high prevalence in hypertensive people with intracerebral haemorrhage. However, reported detection rates of CBAs in histopathological studies vary drastically from study to study, ranging from 5 out of 2800 to 46 out of 100, which may partly reflect differences in study populations as well as challenges in examining hemorrhagic tissue.

KEY FINDINGS: In 4 of the 94 subjects, CBAs were detected in the LSAs.

KNOWLEDGE ADVANCEMENT: We have demonstrated that 7T MRI can detect CBAs in vivo in humans. This technique could allow further longitudinal studies to determine the true prevalence and prognostic significance of CBAs.

INTRODUCTION

Introduction Charcot-Bouchard Aneurysms (CBA) are tiny aneurysms (typically 0.05-2.5 mm in diameter) arising from small perforating arteries (typically < 0.3 mm in diameter), first described by Charcot and Bouchard in 1868.[1] They are most commonly found in the distal

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lenticulostriate arteries (LSA) and post mortem studies have reported a high prevalence in hypertensive people with intracerebral haemorrhage.[2, 3] The rupture of a CBA is a potential cause of subcortical hemorrhage, and case reports have linked the two.[4-8] However, despite the potentially severe consequences of CBA rupture, there is ongoing debate about their existence and prevalence. Reported detection rates of CBAs in histopathological studies vary drastically from study to study, ranging from 5 out of 2800 to 46 out of 100, which may be partly reflect differences in study populations as well as challenges in examining hemorrhagic tissue.[2, 9] Radiological studies offer the advantage of in-vivo whole brain analysis and 3D visualization, but achieving the necessary spatial resolution to detect these small aneurysms, typically 0.05-2.5 mm in diameter,10 has been difficult. A few studies using digital subtraction intra-arterial angiography (DSA) have attempted to identify CBAs but these have been limited to case reports of individual basal ganglia hemorrhage patients,[5-7] and this approach is invasive, thus impractical for larger population studies. Recently, 7T MRI imaging of the small perforating arteries has been demonstrated,[11, 12] providing a much improved resolution compared to 3T. Adding MR contrast has been shown to improve perforator artery visualization further.[13] In this study, we used 7T MRI contrast-enhanced MRA at a spatial resolution of 0.2 mm to determine whether it was possible to detect CBAs in LSA of patients presenting with stroke

MATERIALS AND METHODS

Study population

Subjects with ischemic stroke were recruited from a comprehensive stroke service at Addenbrooke's Hospital Cambridge as a part of the prospective Cambridge 7T Cerebral Small Vessel Disease (CamSVD) study.[13] All stroke subjects from CamSVD were retrospectively identified and included in this analysis. CamSVD is a prospective study aiming at exploring the underlying arterial pathology in cerebral small vessel disease using ultra-high-field 7 Tesla MRI. This recruits patients with lacunar stroke, and also patients with non-lacunar stroke due to presumed cardioembolism or large artery occlusion. Inclusion criteria for the lacunar stroke patients were: a clinical lacunar stroke syndrome (e.g. pure motor stroke, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis or clumsy hand dysarthria syndrome) with an anatomically corresponding lacunar infarct on diffusion weighted imaging (DWI) MRI for acute infarcts (within 3 weeks of symptom onset) or on T1-weighted or fluid-attenuated inversion recovery (FLAIR) images for non-acute infarcts. Inclusion criteria for the non-lacunar group were ischemic stroke with a partial or total anterior circulation ischemic stroke syndrome suspected to be due to large artery atherosclerosis or cardio-embolism.

For both groups exclusion criteria were: 1) Unable/unwilling to consent; 2) Age<18; (3) Monogenic form of stroke such as CADASIL. (4) MRI contraindications e.g. metal objects in or on the body, claustrophobia, pregnancy, known allergy to gadolinium-containing contrast agent, impaired renal function with estimated glomerular filtration rate (eGFR) <59ml/min/1.73m^2 (6). Severe stroke (NIHSS score ≥16); (7) Other major neurological diseases; 8) Severe systemic diseases such as heart failure, liver failure and kidney failure or any illness in the judgement of the investigator that could affect participation in the study.

Additional exclusion criteria for the lacunar group were: 1) Stroke etiology due to cardio-embolism (as defined according to the TOAST criteria[14]) or large vessel disease (>50% stenosis in extra- or intra-cranial cerebral arteries on NASCET criteria[15]); 2) Lacunar infarcts >1.5cm – as many of these infarcts are caused by embolism; 3) Evidence of cortical infarct of any size. Additional exclusion criteria for the non-lacunar group were: presence of a lacunar infarct.

Clinical information and vascular risk factors were collected upon admission, including age, sex, hypertension, hyperlipidemia, diabetes mellites, ischemic heart disease, atrial fibrillation and previous stroke history status. The study was approved by the Institutional Review Board of East of England–Cambridge Central Research Ethics Committee (REC Ref: 19/EE/0219). Written informed consent was obtained from all participants.

MR imaging protocol

A 3D Time-of-Flight (ToF) MRA technique was performed on a whole-body human 7 T MRI scanner (7 T Terra, Siemens Healthineers, Erlangen, Germany) equipped with a single transmit 32-channel receive coil (Nova Medical, Wilmington, Massachusetts). Before image acquisition, a 20 gauge intravenous cannula was inserted in the antecubital vein, and 0.1 mmol/kg of a gadolinium-based contrast agent (Gadobutrol, Gadovist®, Bayer PLC, Reading, UK) [16](Website) followed by 10 millilitres of 0.9% sodium chloride flush was manually injected. After a delay of two minutes, MRA images were acquired with the following parameters: Field of view (FOV) 200 × 156.3 mm^2, centered around the middle cerebral arteries. Voxel Size 0.24 × 0.24 × 0.32 mm^3, TR = 13 ms, TE = 5.1 ms, and nominal flip angle (FA) = 20°. GeneRalized autocalibrating partially parallel acquisition acceleration factor = 2. Two slabs were used with 80 slices per slab to shorten the time of flight of inflowing blood to increase the signal from this blood. Anatomical images including a T1-weighted sequence, T2-weighted sequence, T2-weighted fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted sequences, were also obtained as previously described.[13] The parameters for the T1 image were: FOV = 206 × 206 mm^2, voxel size = 1.1 × 1.1 × 1.0 mm^3, repetition time (TR) = 4300.0ms, echo time (TE) = 1.84ms. T2 FLAIR image: FOV = 230 × 172.5 mm^2, voxel size = 0.4 × 0.4 × 3 mm^3, TR = 9000ms, TE = 68ms. And for DWI image: FOV = 220 × 220 mm^2, voxel size = 2 × 2 × 2 mm^3, TR = 5100ms, TE = 41.0ms. DANTE sequence: FOV = 240 × 175 mm^2, voxel size = 0.5 × 0.5 × 0.5 mm^3, TR = 2620ms, TE = 164.0ms.

Radiological Analysis

MRA images were independently reviewed by 2 experienced neuroradiologists with 9 and 10 years experience (Y.J. and P.B.) to identify CBAs. The search was limited to the bilateral LSA, excluding aneurysms on other vessels from the study. FMRIB Software Library (FSL) image viewer FSLeyes[17] was used to examine the MRA data. Maximum intensity projected (MIP) images with the window length adjusted to optimize visualization of each single LSA vessel were used in combination with the original data. The vessel was then observed from axial, sagittal, and coronal planes to identify potential CBAs. When the in-plane view was unclear, the 3D Slicer[18] volume rendering module was utilized for 3D visualization. In case of discrepancy between the radiologists, consensus was reached through discussion and confirmation by a third independent experienced neuroradiologist with 17 years experience (A.D.M). CBA was defined as a saccular outpouching from the parent vessel or a focal dilatation more than twice the diameter of the parent vessel. Cases where there are faint or

suspected branches originating from the dilatation were classified as infundibula. The diameters of the parent vessels and the maximum diameters of the CBAs were measured, with parent vessel diameters taken at a point just before the CBA. Subjects were then categorized into CBA(+) and CBA(-) groups based on whether at least one CBA was found on their LSA.

Statistical Analysis

Due to the small number of subjects with CBAs and the non-numerical nature of the risk factors data, non-parametric two-sample Wilcoxon-Mann-Whitney tests were used to determine whether the distribution of clinical information and vascular risk factors differed between the CBA(+) and CBA(-) groups. We also compared our reported prevalence rate with the previously highest and lowest reported prevalence rate using Chi-square analysis to determine whether there are significant differences.[2, 9] MATLAB R2023b[19] on a Windows platform was used to conduct the statistical analysis.

RESULTS

94 subjects were recruited of whom 75 had lacunar stroke and 19 had non-lacunar stroke. Of the 94 subjects, CBAs in the LSA were identified in 4 patients. Characteristics of patients with and without CBAs are shown in Table 1. There was no significant difference between the two groups. Among the 4 CBA(+) subjects, 2 were in the lacunar infarct group and 2 in the non-lacunar infarct group, One of the subjects in the lacunar stroke group had 2 CBAs and the rest each had 1 CBA. The diameter of the parent vessel ranged from 0.26mm – 0.37mm, and the maximum diameter of the CBA ranged from 0.73mm – 1.39mm. In one of the lacunar stroke subjects, the CBA was on the vessel adjacent and potentially supplying to the lacunar infarct, suggesting a potential association between the aneurysm and the infarct. (Supplementary Table. Fig 1. And Fig 2.) In one subject the aneurysm was at the LSA bifurcation. In the other cases the aneurysm was identified at a non-branch point.

Table 1: Clinical information and vascular risk factors.

Column A	Overall	CBA(+) group	CBA(-) group	P value (W-M test)
n	94	4	90	
Lacunar stroke (n)	75	2	73	
Non-Lacunar stroke (n)	19	2	17	
Age (Mean)	65.55	59.50	65.82	0.59
Sex(Female %)	28.72%	0	30.00%	0.20
BMI	28.48	30.15	28.4	0.19
Smoking history (% of ever smokers)	50.00%	25.00%	51.11%	0.31
Alchohol Intake (% of ever drinkers)	54.35%	50.00%	54.55%	0.91
Fazekas Score (Mean)	1.27	0.75	1.3	0.25
Hypertension (% with hypertension)	67.02%	25.00%	61.43%	0.07
Hyperlipidaemia (% with hyperlipidaemia)	57.45%	25.00%	55.71%	0.18
Diabetes Mellitus (% with diabetes mellitus)	19.15%	0	21.42%	0.33
Ischemic Heart Disease (% with ischemic heart disease)	4.25%	0	5.71%	0.68
Atrial Fibrillation (% with atrial fibrillation)	6.38%	25.00%	5.71%	0.13
Peripheral Vascular Disease (% with peripheral vascular disease)	0	0	0	NA*
Previous Stroke (% with previous stroke)	14.89%	0	18.57%	0.4

W-M test: Wilcoxon-Mann-Whitney tests between Charcot-Bouchard Aneurysms (CBA)(+) and CBA(-) group
*: NA due to neither the CBA(+) nor CBA(-) groups had any subjects with peripheral vascular disease, resulting in two identical datasets, which the W-M test cannot process.

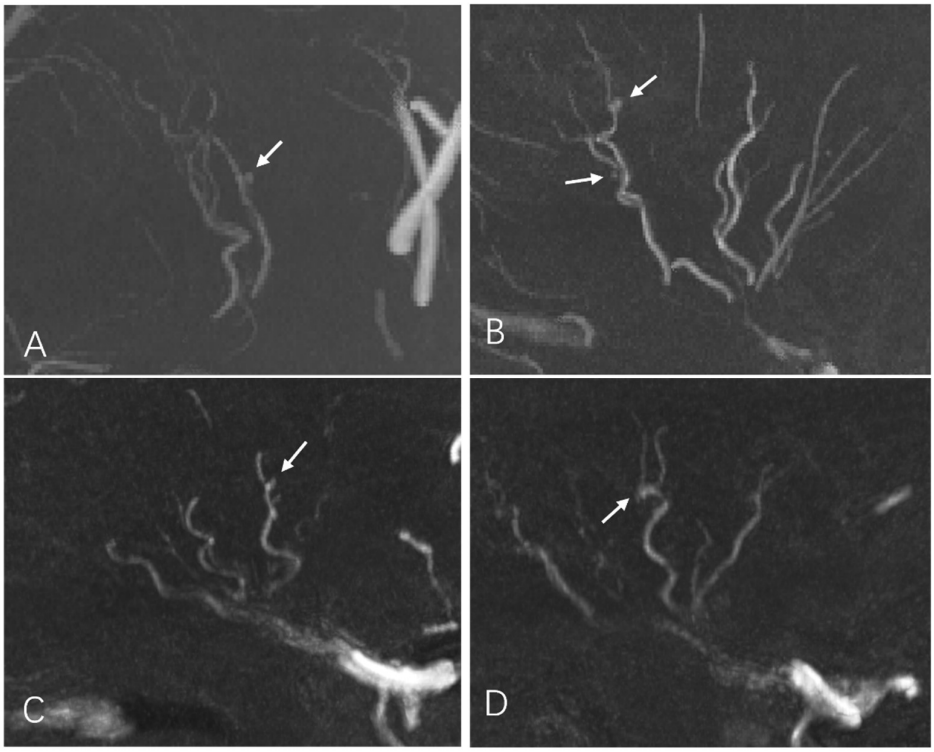

FIG 1. Demonstrating the 4 subjects found with Charcot-Bouchard Aneurysms (CBA). A) 69 y-o male with lacunar stroke on the right putamen and corona radiata, CBA found on the left lenticulostriate arteries (LSA). B) 36 y-o male with lacunar stroke on the right putamen and corona radiata, 2 CBAs on the right LSA. C) 75 y-o male with non-lacunar stroke on the left temporal lobe, CBA on the right LSA. D) 58 y-o male with non-lacunar stroke on the left frontal lobe, CBA on the right LSA.

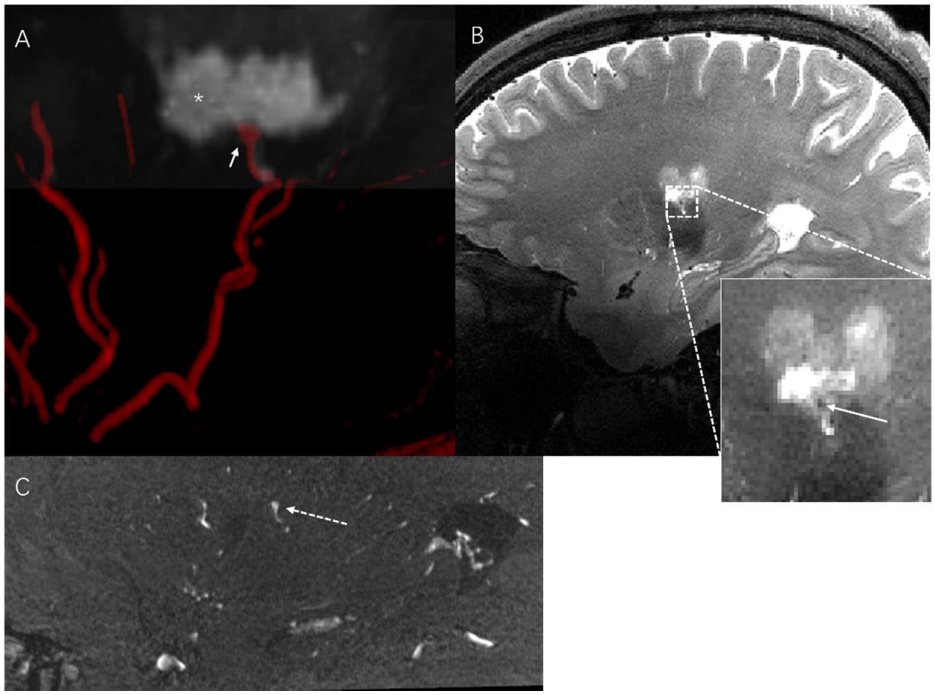

FIG 2. Close proximity of a Charcot-Bouchard Aneurysms (CBA) with the lacunar infarction in a 36 y-o male subject. A: 3D MIP view of the DANTE sequence overlayed on the MRA sequence. MRA is colored red for better visualization. Lacunar infarction can be seen as the patch of hyperintensity (*) and the CBA is adjacent to it (short arrow) on the possible responsible vessel. B. Sagittal view of the DANTE sequence, the black blood signal can be seen (Long arrow). C. Sagittal view of the MRA sequence, the CBA is visible (Dash arrow).

In some cases, there appeared to be CBA on initial review, but on closer examination in 3D the feature was seen to be a loop of the LSA, (see Fig 3, also supplement Video 1), and not an aneurysm. Our reported prevalence (4/94) is significantly higher than previously reported lowest value we can find[9] (5/2800, P = 1.53e-09) and significantly lower than the highest value we can find[2] (46/100 hypertensive subject, P = 9.214e-11).

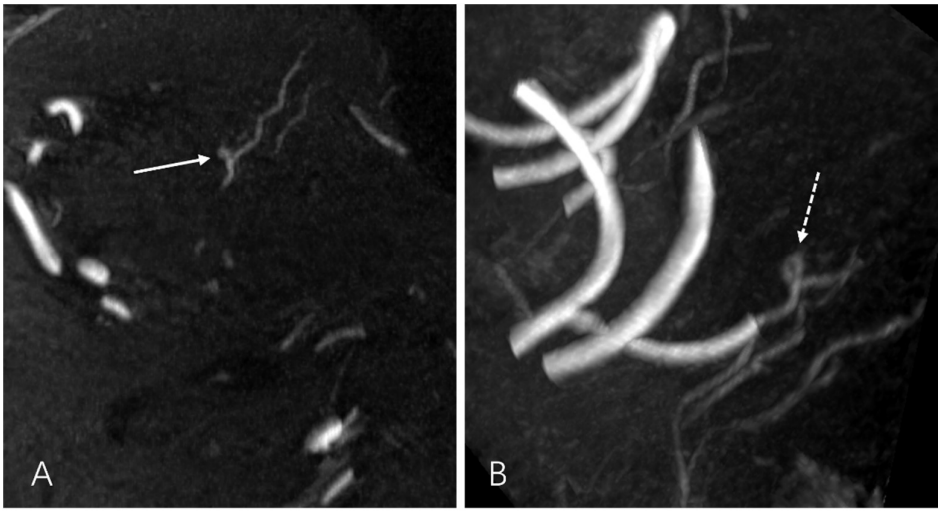

FIG 3. Potential pitfalls in identifying Charcot-Bouchard Aneurysms (CBA). A. Coronal view suggested a CBA on lenticulostriate arteries (LSA) (Arrow), B. With 3D representation, the suspected CBA was found to be a looped LSA (Dash arrow). Also see supplement video 1.

DISCUSSION

Using 7T MRI we were able to detect CBAs in vivo in humans. We detected them in 4 of 94 patients with stroke. The diameter of the parent vessel ranged from 0.26mm – 0.37mm, and the maximum diameter of the CBA ranged from 0.73mm – 1.39mm.

The diameters of the CBAs and their parent arterioles found in our study are generally consistent with previously reported values (0.05-2.5 mm for CBAs and less than 0.3 mm for parent arterioles, respectively). This suggests that the size and location of the CBAs we identified align with findings from previous autopsy studies. Identification of CBAs in MRA is challenging because distal aneurysms may not be visualized due to signal loss in the distal sections of the LSAs on MRA. However, this study's use of gadolinium contrast has enabled clearer visualization of these distal regions compared to MRA without contrast.

Although this is an only a moderate sized cohort, the prevalence of subject with CBAs we found is higher than that reported in previous autopsy studies[9, 10] which identified 5 in 2800 cases. This may partially reflect the difficulty of sampling from the whole brain in autopsy studies. For example, in one typical autopsy study by Shino et al.[10] representative sections from several brain regions were sampled, which could underestimate the prevalence when compared to a whole region analysis like our MRA method. It may also be caused by the high rates of hypertension in our cohort. Hypertension has previously been suggested to be a major risk factor for CBAs.[2] In contrast to the autopsy studies, earlier radiographic studies, which used X-ray imaging to examine brain slices injected with a barium sulfate and gelatin mixture in the arteries, reported a higher prevalence, as high as 46 out of 100 subjects in hypertensive group.[2] However this could reflect an over-reporting because these studies relied on single-plane imaging. This approach can lead researchers to mistakenly identify arteriolar loops and twists as CBAs as also noted in our study and illustrated in Figure 3. The use of 3D MRA in our study allowed differentiation between looped LSAs and true CBAs. (Fig 3. And supplement video 1)

The clinical significance and predictive value of CBA remains to be determined. In our study the 4 subjects with CBAs all had certain degree of vascular risk factors. 1 subject (75 y-o) had hypertension. Among the rest of the 3 subjects, 1 (58 y-o) had hyperlipidaemia, 1 (69 y-o) had more extensive WMH (Fazekas = 2). The rest 1 is an adult (36 y-o) with lacunar infarction in basal ganglia, he had BMI of 32.7 and is a current smoker. Hypertension, hyperlipidaemia, cerebral small vessel diseases and smoking history have all been previously proposed as a risk factor of intracranial aneurysms.[20-22] But due to the small sample size, whether these risk factors are really associated with CBA is uncertain and requires larger cohorts to confirm.

However now we have demonstrated that they can be detected in vivo in humans using 7T MRI, this offers the opportunity to perform larger studies to correlate their presence with clinical factors, and longitudinal studies to determine their predictive significance. It is possible that thrombus associated with a CBA could contribute to lacunar stroke particularly if the CBA is at a branch point. Supporting this we noted one CBA very close to a lacunar infract with no evidence of haemorrhage thereby excluding aneurysm rupture. (Fig 2.) More evidence comes from previous autopsy studies also shown that organized thrombosis in the CBA could cause downstream lacunar infarction.[23] This finding potentially making CBA an important small image features only accessible by 7T MRI.[24] Future longitudinal studies or autopsy studies in patients with lacunar infarction could provide further insights into this potential link.

There are several limitations to our study. Although this was a large sample size for a 7T study with 94 stroke patients imaged, only four had CBA. This small number means we cannot draw robust conclusions in risk factors associated with CBA or their true prevalence. Also, our study populations are limited to stroke and cerebral small vessel disease subjects, so we cannot be sure whether the prevalence

found in our study would be different from that in a general population. Thirdly, to acquire data in a reasonable acquisition time we limited the field of view to area around MCA, thus parts of the cortical perforating arterioles are not included in the field. The scanning time of the sequence is 9 min 53 seconds with acceleration, which is relatively long. Prolonging the scanning time could prove difficult especially in the elderly stroke patients. This means we may have missed CBAs at other locations outside the field of view. Lastly, our study lacks a golden standard for CBA detection. Ideally LSAs detected on 7T should be validated against intra-arterial DSA and histopathology at autopsy. However, DSA could not be performed as part of the research evaluation for ethical reasons due to the associated stroke risk and no patient had it performed as part of the clinical care. No patients had autopsy data available. Further studies are needed in this area.

CONCLUSIONS

In conclusion we have shown it is possible to detect CBAs in vivo in humans using 7T MRI. Further studies combining 7T MRA and autopsy are needed to validate the result. This technique will allow future studies to determine their frequency in different stroke cohorts, and their prognostic significance.

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SUPPLEMENTAL FILES

Supplementary Table: Information of the 4 CBA(+) subjects.

Subject Number	Age	Sex	Number of CBAs	CBA location	Max diameter	Diameter of parent vessel	Clinical characteristics
1	69	Male	1	Left LSA	0.73mm	0.26mm	Left sided face droop and slurred speech. Lacunar stroke in the right putamen and corona radiata.
2	36	Male	2	Right LSA	1.39mm	0.38mm	Left sided facial droop and slurred speech. Lacunar stroke in the right putamen and corona radiata.
					0.88mm	0.25mm	CBA was adjacent to the infarct site. No evidence of old hemorrhage on susceptibility weighted sequences
3	75	Male	1	Right LSA	1.13mm	0.37mm	Dysphasia. Cortical infract in left temporal lobe.
4	58	Male	1	Right LSA	0.92mm	0.33mm	Expressive dysphasia. Cortical infarct in left frontal lobe.

CBA: Charcot-Bouchard Aneurysms; LSA: lenticulostriate arteries

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1,2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4,5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7,8
Bias	9	Describe any efforts to address potential sources of bias	7,8
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	8

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8,9
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	*8,9*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8,9
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title page

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.