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Cortical Localization of Microbleeds in Cerebral Amyloid Angiopathy: An Ultra High-Field 7T MRI Study

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Abstract

The extent of cortical involvement of cerebral amyloid angiopathy (CAA)-related microbleeds (CMBs) remains unclear. We examined five consecutive patients with probable CAA and three non-demented elderly subjects with ultra-high field 7T MRI, to identify the precise location of CAA-related CMBs. In five CAA patients, 169 of a total of 170 lobar CMBs were located in cortical areas on 7T MRI, while a precise cortical versus juxtacortical localization was unable to be determined for 50/76 CMBs observed by conventional MRI. 7T MRI demonstrates that nearly all lobar CMBs are located in cortex in CAA.

Keywords

Cerebral amyloid angiopathy; cerebral microbleed; cortex; magnetic resonance imaging; ultra-high field

INTRODUCTION

Cerebral amyloid angiopathy (CAA) is a common age-related cerebral small vessel disease characterized by progressive deposition of amyloid- β (A β) protein in the walls of cortical and leptomeningeal arteries which can cause large lobar hemorrhages, cerebral microbleeds (CMBs), and superficial siderosis [1, 2]. CAA appears to be an important cause of cognitive decline in the elderly [1]. Although CAA-related CMBs have been shown to be preferentially located in lobar brain regions, the extent of cortical involvement of these small

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SUPPLEMENTARY MATERIAL

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hemorrhagic lesions remains unclear. Previous pathologic studies have demonstrated A β protein deposition in cortical and leptomeningeal vessels in CAA [3] and recent neuroimaging evidence suggests that CMBs occur in areas of amyloid deposition [4]. Based on these data, it is possible that the hemorrhagic manifestations of the disease in the cortex are considerable.

Ultra-high field magnetic resonance imaging (MRI) techniques may improve detection of these hemorrhagic manifestations and consequently allow for higher sensitivity in CAA diagnosis [2, 5, 6]. A recently published study showed that 7T MRI was superior in identifying CMBs in patients with atherosclerotic disease compared with 1.5T MRI of the same 3 mm thickness [7]. Additionally, given its high signal-noise ratio and its ability to achieve high spatial resolution, ultra-high field 7T MRI also offers the advantage of clear gray-white matter differentiation and thus may serve to better visualize cortical pathology in CAA [8].

We thus sought to investigate 1) whether 7T MRI allowed for better visualization of CMBs in CAA, and 2) the extent of cortical involvement of these hemorrhagic lesions. We hypothesized 7T-MRI would identify an increased number of CAA-related lobar CMBs in cortical areas with less involvement in the juxtacortical areas.

METHODS

We recruited five consecutive patients with probable CAA identified using the modified Boston criteria [2] from an ongoing single-center prospective longitudinal cohort of CAA. They fulfilled the following criteria: 1) diagnosis of probable CAA; 2) no contraindication for 7T MRI; and 3) informed consent for study participation. Non-demented elderly subjects without CAA of comparable age and cognitive status were recruited from the memory clinic in the Massachusetts Alzheimer's Disease Research Center at our institution. This study was performed with approval and in accordance with the guidelines of the Institutional Review Boards of Massachusetts General Hospital. Written informed consent was obtained in all subjects. Demographic and clinical data are provided in Table 1.

MRI acquisition and analysis

7T protocol for this study—Subjects were scanned with a 7T whole-body scanner (Siemens Healthcare, Erlangen, Germany) using an SC72 gradient set, providing a gradient amplitude of 70 mT/m and a maximum slew rate of 200 T/m/s. Due to the size constraints of the 32-channel head coil of 7T scanner, patient recruitment was limited by head size (maximum head circumference of 58 cm). Additionally, for elderly CAA subjects with cognitive impairment, the prolonged scan time in the 7T bore tube (twice that long as lower-field strength bore tubes) triggered claustrophobia more easily and thus limited recruitment.

We used an in-house single channel volume coil for RF transmission and an in-house 32-channel phasedarray coil for reception [9]. At the beginning of the 7T scan session, multiple B_0 shimming was performed to minimize susceptibility effects. A B_1 -map was acquired ('actual flip angle image' method) after manual shimming and before acquiring the T2* images. Based on the B_1 -map, we estimated the voltage to target the desired flip angle at the

cortical area of the brain. Images from T2*-weighted 2D Fast Low Angle Shot (FLASH) spoiled gradient-echo (GRE) images were obtained with the following parameters: TR = 1690 ms, TE = 6.34+3.2n [$n = 1, \dots, 9$], flip angle: 55°, in-plane resolution = 330 $\mu\text{m} \times 330 \mu\text{m}$, 1 mm slice thickness (25% gap), 40 slices, matrix = 576 $\times$ 504, field-of-view: 192 mm $\times$ 168 mm, band width = 335 Hz/pixel, GRAPPA acceleration factor = 2 (with 32 ACS lines), and an acquisition time of 7.56 min.

In addition, subjects also underwent either 1.5T with repetition time 750 ms, echo time 25 ms, flip angle 20° and slice thickness 5 mm or 3T with parameters as previously described [10] research MRI with T2*-weighted sequences to identify CMBs at the same day with 7T.

CMB detection—CMBs were defined as small, homogeneously hypointense round or ovoid lesions on T2*-weighted MRI sequences, distinct from other potential mimics such as calcification or air-bone susceptibility-related artifacts [6]. The number and location of lobar CMBs were recorded by two experienced readers (JN and EA) blinded to all clinical data. Presence and location of CMBs were determined by consensus. Although we did not perform inter-rater reliability in this sample due to the limited sample size, CMBs were classified as either cortical or juxtacortical in location. Lesions were considered as cortical if greater than 50% of the lesion was located in the cortical gray matter. Lesions were manually labeled. Discordant readings were resolved by consensus. Additionally, we calculated the interrater concordance for CMB location (cortical versus juxtacortical) on all identified CMBs with a third rater, blind to the study hypothesis. We showed a high interrater correspondence (intraclass coefficient = 0.9983).

CMB co-registered to a common space—In order to determine the cortical location and distribution of CMBs in the brain, gradient-echo (GRE) scans of the five CAA subjects examined-along with their corresponding lesions were co-registered to a common space using the affine registration tool of the FMRIB Software Library (FSL) [11–17]. A total of 170 lesions were identified. CMBs were identified using similar methods for conventional MRI-based CMB detection as previously described [6, 18]. As in lower field studies, CMBs were identified as round hypointense lesions on T2*-weighted imaging. As in our previous reports, hypointense lesions were excluded if they appeared to be vascular flow voids (based on sulcal location or linear shape), basal ganglia mineralization, or artifact from adjacent bone or sinus [19, 20].

RESULTS

A total of 171 lobar CMBs were detected by 7T MRI compared with 77 by conventional MRI. Among the three non-CAA subjects, only one CMB was found (Subject 3) and was located in the periventricular white matter. Due to clear differentiation of gray matter areas from juxtacortical white matter areas achieved using our ultra-high field technique, CMBs were readily localized either in the cortex or in the adjacent white matter on 7T imaging. In the five patients with probable CAA, 169/170 (99%) lobar CMBs were definitively located in cortical gray matter by 7T-T2*-weighted MRI, while only 25/76 (33%) lobar CMBs were identified to be in cortical gray matter by 1.5 MRI. A precise cortical versus juxtacortical localization was unable to be determined for 50/76 CMBs observed by conventional MRI.

Figure 1 illustrates the cortical localization of CAA-associated CMBs in this cohort. Figure 2 illustrates the typical cortical location of CAA-related CMBs in 7T compared with conventional MRI T2* sequences. We also have included a Supplementary figure to further illustrate the intracortical location of CMBs in our five CAA patients.

DISCUSSION

In patients with CAA, this ultra-high field 7T T2*-weighted MRI study demonstrates better detection of CMBs and also shows that nearly all lobar CMBs are located in cerebral cortex and not in the juxtacortical white matter.

Our results may point to the nearly exclusive cortical distribution of lobar CMBs in patients with CAA. These hemorrhagic manifestations in the cortex, taken together with other cortical pathologies such as microinfarction and brain atrophy, may play an important role in cognitive decline patients with CAA. Interestingly, the exact location of most of these cortical CMBs was not clearly identified by conventional MRI scans, in line with previous reports. The present results are consistent with pathological findings demonstrating that A β deposition in CAA predominantly affects cortical and meningeal vessels versus vessels in the white matter [3]. This is in contrast to the deep or infratentorial location of vascular pathology in other small vessel diseases such as hypertension-related small vessel disease or CADASIL. However, although our results give new insights into the localization of CAA-related CMBs, the specific cerebral arteries implicated in symptomatic intracerebral hemorrhage in CAA remain unclear. A small pathological study of six patients with CAA suggested that ruptured meningeal vessels, and not vessels in the cortex, may be associated with large lobar hemorrhage in the disease [21]. The implications of our CMB findings in regards to the development of future symptomatic intracerebral hemorrhage in CAA remains to be defined in future work.

In addition, this study demonstrates that the detection of visualization of CMBs is superior at 7T MRI compared to 1.5T, which is consistent with previous studies which suggests CMB detection strongly depends on MRI parameters [6]. The “new” lesions seen only at 7T were all detected in lobar areas (and not deep structures or other locations) consistent with known microbleed distribution in CAA [5]. This may suggest that these lesions are less likely to be artifacts of the ultra-field technique, but are rather CAA-related CMBs that were undetected at lower field strength.

Our study has limitations. In order to obtain the highest in-plane resolution of ultra-high field T2*-weighted images, we were unable to obtain full brain coverage on 7T scans due to exceedingly long scan duration. However, as the aims of this study were to explore the sensitivity of 7T MRI for hemorrhagic manifestations of CAA and to identify the precise location of lobar CMBs in disease rather than assess total CMB burden, it is unlikely that this limitation would significantly alter our results. It is possible that we did not detect a greater proportion of juxtacortical CMBs in CAA either due to limited brain coverage discussed above or due to the small sample size of our study. However, the latter may not significantly contribute to bias as we identified 170 lobar CMBs on 7T scans in the CAA patients in this study. It is conceivable that through co-registration of 3D T1 images to T2*-

weighted images on conventional MRI, we could have potentially assessed cortical location of CMB more reliably at lower field strength. While this secondary image analyses using conventional MRI was not the goal of current study, the reliability of CMB localization using this method would be important to assess in future studies of CMB in CAA. Finally, it is possible that small blood vessels or calcifications were misclassified as CMBs due to ultra-high field 7T MRI being very prone to artifacts. However, as our aim was to identify the precise location of CMBs in CAA but not to determine exact number, this would be less likely to affect our results. Furthermore, our use of established criteria [6] in identifying CMBs also makes this possibility less likely.

In conclusion, ultra-high field 7T MRI in patients with CAA demonstrates that nearly all lobar CMBs are located in the cerebral cortex in the disease. Further studies should examine the correlation between cortical CMBs and cognitive decline in patients with CAA.

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Fig. 1.

Microbleed distribution in all five patients with CAA (all scans were coregistered): The 6 axial 1-mm 7T slabs ($330 \times 330 \mu\text{m}$ in-plane resolution) demonstrate the distribution of 135 of the 170 lesions in 5 CAA patients (the remaining 35 lesions were located in the other 34 slabs not shown in the figure). Lesion markers were placed at the center of the marked lesion after image resampling and do not represent the actual size of the lesion. 7T = 7 Tesla.

Fig. 2.

Typical distribution of CAA-related CMBs on ultra-high field MRI compared with conventional MRI. A and B, GRE of subject 8:1.5T (A) and 7T (B) sequences show multiple CMBs in the right hemisphere (panes); C and D, GRE of subject 4:1.5T(C) and 7T (D) scans show 2 CMBs in the left hemisphere (panes). Panels A1–D1 demonstrate magnification of lesions seen in panels A–D, respectively (black arrows). Due to the different thicknesses and flip angles between 1.5T and 7T scans, the slices in both scans are not exactly the same. GRE = Gradient Echo; 1.5T = 1.5 Tesla; 7T = 7 Tesla.

Table 1

Demographic, clinical and imaging information of all subjects

Characteristic	Subjects							
	1	2	3	4	5	6	7	8
Age	66	76	82	67	57	69	68	72
Gender	M	F	F	M	M	M	M	M
CAA	–	–	–	+	+	+	+	+
Symptomatic ICH	–	–	–	+	+	–	+	–
History of hypertension	+	+	–	+	–	–	+	+
Cognitive decline	+	+	+	+	–	+	–	–
Number of CMBs by 7T	0	0	1	31	5	15	26	93
Number of CMBs by 1.5/3T	0	0	1	6	5	3	8	54

CAA, cerebral amyloid angiopathy; ICH, intracerebral hemorrhage; CMBs, CAA-related microbleeds.