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MRI and CT imaging biomarkers of cerebral amyloid angiopathy in lobar intracerebral haemorrhage

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ABSTRACT

Background. Cerebral amyloid angiopathy (CAA), a common cause of intracerebral haemorrhage (ICH), is diagnosed using the Boston criteria including MRI biomarkers (cerebral microbleeds [CMB] and cortical superficial siderosis [cSS]). The simplified Edinburgh criteria include CT biomarkers (subarachnoid extension [SAE] and finger-like projections [FLP]). The underlying mechanisms and diagnostic accuracy of CT compared to MRI biomarkers of CAA are unknown.

Methods. We included 140 survivors of spontaneous lobar supratentorial ICH with both acute CT and MRI. We assessed associations between MRI and CT biomarkers and the diagnostic accuracy of CT- compared to MRI-based criteria.

Results. FLP were more common in patients with strictly lobar CMB (44.7% vs 23.5%; p=0.014) and SAE was more common in patients with cSS (61.3% vs 31.2%; p=0.002). The high probability of the CAA category of the simplified Edinburgh criteria showed 87.2% (95%CI 78.3-93.4) specificity, 29.6% (95%CI 18.0-43.6) sensitivity, 59.3% (95%CI 38.8-77.6) positive predictive value and 66.4% (95%CI 56.9-75.0), negative predictive value, 2.3 (95%CI 1.2-4.6) positive likelihood ratio and 0.8 (95%CI 0.7-1.0) negative likelihood ratio for probable CAA (*vs* non-probable CAA), defined by the modified Boston criteria; the area under the receiver operating curve (AUROC) was 0.62 (95%CI 0.54-0.71).

Conclusion. In lobar ICH survivors, we found associations between putative biomarkers of parenchymal CAA (FLP and strictly lobar CMBs) and putative biomarkers of leptomeningeal CAA (SAE and cSS). CT biomarkers might help rule-in probable CAA (diagnosed using the Boston criteria), but their absence is probably not useful to rule it out, suggesting an important continued role for MRI in ICH survivors with suspected CAA.

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INTRODUCTION

Spontaneous lobar intracerebral haemorrhage (ICH) related to cerebral amyloid angiopathy (CAA) is associated with high risks of death, poor functional outcome, dementia [1] and intracerebral hemorrhage (ICH) recurrence [2], so it is important to identify in clinical practice. Histopathological assessment is the reference standard to identify CAA, but cerebral tissue is rarely available, so neuroimaging biomarkers are usually used to infer the presence of CAA. The modified Boston criteria for CAA [3][4] are widely used MRI-based criteria. However, MRI is not always available, tolerated, or possible due to contraindications, particularly during acute care.

More recently, the acute CT-based Edinburgh criteria have been proposed [5]; a CT-only version of the criteria (the simplified Edinburgh criteria) include only subarachnoid extension (SAE) and finger-like projections (FLP). The Edinburgh criteria demonstrated excellent diagnostic accuracy for autopsy-proven CAA in severe ICH (fatal events), but still require external validation. Furthermore, little is known about the underlying mechanisms of FLP or SAE. FLP might reflect CAA affecting brain parenchymal small vessels (causing blood to dissect into abnormal brain tissue), while SAE might be due to leptomeningeal arteriolar CAA (leading to acute bleeding into the subarachnoid space).

We aimed to evaluate: (1) whether FLP are associated with CMBs (as a putative biomarker of parenchymal CAA); (2) whether SAE is associated with cSS (as a putative biomarker of leptomeningeal CAA); and (3) to evaluate the diagnostic accuracy and concordance of simplified Edinburgh criteria compared to modified Boston criteria.

METHODS

We retrospectively included consecutive adult patients with spontaneous (non-traumatic) ICH from: an observational prospective multicenter cohort study (Clinical Relevance of Microbleeds in Stroke; CROMIS-2 [ICH] - NCT02513316 [6]) and from the SIGNaL register (Stroke InvestiGation in North and Central London). We included patients with ICH and both CT and MRI performed after the index event. Exclusion criteria were: age < 55 years; and non-lobar, infratentorial or secondary ICH (Figure 1). We reported the study in accordance with STARD reporting guidelines. [7] [8] Measurement of

ICH volume was performed on CT scans via a semi-automated approach [9] and on MRI by manual segmentation on SWI sequences. ICH location was assessed using the Cerebral Haemorrhage Anatomical RaTing inStrument (CHARTS) [10].

All neuroimaging biomarkers were rated by a single trained rater, blinded to other clinical and neuroradiological data. Observers evaluated CT for FLP and SAE as previously described [5] after attending a web-based training module (www.ed.ac.uk/edinburgh-imaging/ecciting). Each patient was categorized for the probability of CAA using the simplified Edinburgh criteria (with a high probability defined by the presence of both FLP and SAE) [5] In the derivation study [5], no participants had FLP in isolation, but given the strong association between CAA and FLP [5] we classified FLP in isolation as intermediate risk of CAA. To obtain inter-rater reliability a random sample of 19 CT scans (SIGNaL cohort) was rated by a blinded experienced Stroke Neurologist (DJW).

CMBs and cSS were rated on T2*-weighted gradient-recalled echo (GRE) or susceptibility-weighted imaging (SWI) using a validated rating scale [11] and per consensus criteria [12][13], respectively. The typical appearance of cSS (“track-like” low signal in the subpial layers of cortex either side of the sulcus) and the distance in space from the symptomatic ICH were used to distinguish cSS from acute convexity subarachnoid haemorrhage (SAH). No patients with isolated convexity SAH were included. Each patient was categorized using the modified Boston criteria [3]. We compared the probable CAA category to all other lobar ICH (namely, non-probable CAA: including possible CAA and lobar ICH not meeting the criteria for CAA [i.e. patients with no additional haemorrhagic CAA markers (lobar CMBs or cortical siderosis) or ≥ 1 deep CMB]). From the CROMIS-2 cohort a random 10% sample (149 scans) was rated to quantify intra-rater and inter-rater reliability for CMBs. For cSS presence the entire cohort of patients included in the SIGNaL cohort (42 scans, 30% of the entire cohort) were rated twice for intra-rater reliability.

Univariate analysis was performed to evaluate association between variables and categories; the strength of associations was quantified via agreement proportion and kappa (k) values. The diagnostic accuracy of a high probability of CAA (according to the simplified Edinburgh criteria) in predicting probable CAA (according to the modified Boston criteria) was assessed by calculating the

area under the receiver operating characteristic curve (AUROC), sensitivity, specificity, positive and negative predictive values. Positive and negative likelihood ratios (LR+ and LR-) were also calculated. Univariable and multivariable (adjusted for age and sex) linear regression analysis was performed to assess if presence of CT (SAE or FLP) and MRI (strictly lobar CMB or cSS) biomarkers of CAA were correlated with ICH volume. To test for selection bias, we compared (univariate analysis) patients with and without available MRI. Inter/intra-observer variability of ratings was calculated using the Cohen κ statistic. The significance level was set at p=0.05. Statistical analysis was performed using STATA 16 (StataCorp. 2019 *Stata Statistical Software: Release 16*).

Standard Protocol Approvals, Registrations and patient consents. Written informed consent was obtained from all participants in CROMIS-2 (approved by UK National Health Service Research Ethics Committee: 10/H0716/64); in case of lack of capacity written informed consent was obtained from a relative or representative. For the SIGNaL cohort, data were collected as part of routine clinical care and data analysis was approved as a service evaluation by the University College London Hospitals NHS Trust Data Governance Review Board.

Data Availability Statement. All de-identified participant data requests should be submitted to the corresponding author for consideration by the CROMIS-2 and SIGNaL Steering Committees.

RESULTS

We included 140 adult patients with spontaneous lobar supratentorial ICH. Baseline characteristics, neuroimaging variables and classifications according to the Edinburgh and Boston criteria are reported in Table 1.

Associations between CT and MRI biomarkers (with agreement proportion and k values) are reported in Table 2. FLP presence was associated with CMB presence (35.8% vs 20.3%; p=0.047), strictly lobar CMBs (44.7% vs 23.5%; p=0.014) and total CMB count (p=0.013). FLP were not significantly more common in patients with cSS (35% vs 27.5%; p=0.390) and were not associated with cSS severity (p=0.691). SAE was more common in patients with cSS (61.3% vs 31.2%;

p=0.002), and was associated with cSS severity (p=0.002). SAE was not significantly associated with CMB presence (37% vs 39%; p=0.815), strictly lobar CMB (47.4% vs 34%; p=0.157) or CMB count (p=0.787).

Compared to patients without probable CAA, FLP were more common in patients with probable CAA (40.7% vs 22.1%, p = 0.018). Compared to patients without probable CAA, SAE was more common in patients with probable CAA (51.9% vs 29.1%, p = 0.007). In both cases the agreement proportion was 63.6% (95%CI 55.0 – 71.5).

Adopting probable CAA based on the modified Boston criteria as the diagnostic reference, a high probability of CAA according to the simplified Edinburgh criteria showed specificity 87.2% (95%CI 78.3–93.4), sensitivity 29.6% (95%CI 18.0–43.6), positive predictive value 59.3% (95%CI 38.8–77.6), negative predictive value 66.4% (95%CI 56.9–75.0), LR+ 2.3 (95%CI 1.2-4.6) and LR- 0.8 (95%CI 0.7-1.0). The discrimination (AUROC) of the simplified Edinburgh criteria (high probability vs intermediate or low probability), for probable CAA according to the Boston criteria (*vs* non-probable) was 0.62 (95%CI 0.54-0.71) (Table 3).

The median ICH volume was significantly higher when FLP were present (20.4 ml *vs* 7.7 ml; p <0.001) or SAE (16.7 *vs* 6.7 ml; p < 0.001); these differences remained significant after correcting for age and gender (p < 0.001). We found no differences in the presence of cSS and strictly lobar CMBs according to ICH volume. When we assessed the subgroup of patients with ICH volume greater than the median value of our cohort (12.0 mL), the sensitivity of Edinburgh criteria increased from 29.6% (95%CI 18.0–43.6) to 50.0% (95%CI 27.2 - 72.9), while specificity was slightly reduced at 77.4% (95%CI 58.9 - 90.4).

Comparison between patients with and without available MRI (Table e1) and intra/inter-rater reliability for the presence of CAA biomarkers (Table e2) are reported in Supplementary material.

DISCUSSION

In this study of patients with spontaneous lobar ICH we found significant and specific associations between FLPs and SAE (on CT) and CMBs and cSS (on MRI), respectively. These observations

provide new insights into the mechanisms and anatomical distribution of the underlying CAA pathology: FLPs are likely to represent parenchymal-predominant CAA (indicated by strictly lobar CMBs on MRI), while SAE might reflect leptomeningeal-predominant CAA (indicated by cSS on MRI). We also found that the prevalence of CT biomarkers increased with the degree of diagnostic certainty regarding CAA defined by the modified Boston criteria and with the volume of ICH. CT diagnostic biomarkers for CAA could be useful in everyday clinical practice, but have only been validated in patients who suffered fatal ICH [5]. Our study in ICH survivors showed that the Edinburgh CT-only criteria [5] do increase the likelihood of CAA (defined by the Boston MRI-based criteria), but to a modest extent (LR+ 2.3 [95%CI 1.2-4.6]; a LR+ of more than 3 is considered to be a good test to rule in a disease). Nevertheless, when a diagnosis of CAA is suspected and MRI is not available (i.e. very unwell or claustrophobic patients, non-MRI compatible implanted devices), the presence of both SAE and FLP on CT might help to rule-in CAA but their absence is probably not useful to rule it out (LR- 0.8 [95%CI 0.7-1.0]; a LR- of less than 0.33 is considered a good test to rule out a disease).

The original Edinburgh criteria validation study [5] found that all cases with high or intermediate probability of having moderate or severe CAA were classified as probable CAA by the Boston criteria, but this analysis was available for only 7 patients (with both CT and MRI available). A recent study [14] found that FLP presence (on CT) was significantly more frequent in probable than in possible CAA, but did not specifically examine associations between CT and MRI biomarkers. Our findings are consistent with these previous observations, but also provide new evidence regarding the underlying mechanisms and diagnostic accuracy of the simplified Edinburgh acute CT criteria. Another recent study [15] on Dutch-type hereditary CAA patients documented that the presence of FLP and SAE correlate with ICH volume with higher sensitivity of simplified Edinburgh criteria in large ICH volumes. Our results are in line with this finding: when simplified Edinburgh criteria were applied in patients with ICH volume greater than 12 mL (the median volume), sensitivity increased with only slightly lower specificity. Further studies may be helpful to determine whether a minimum

ICH volume cutoff point should be considered to maximize the diagnostic accuracy of the Edinburgh criteria.

CAA is not a uniform disease, having a complex range of clinical, imaging and neuropathological subtypes [16]. An autopsy-based study described two CAA phenotypes [17]: in CAA type 1, amyloid beta-protein (A-beta) is primarily found in cortical capillaries, while in CAA type 2 A-beta is primarily deposited in leptomeningeal and cortical vessel, sparing cortical capillaries. These phenotypes are hypothesized to be partially driven by APOE genotype: APOE e4 is associated with type 1 (parenchymal-predominant) CAA, while APOE e2 is associated with type 2 (leptomeningeal-predominant) CAA [17]. In line with these recent histopathological observations, two recent meta-analyses found that strictly lobar CMB are related to APOE e4 [18] and that cSS is most strongly associated with APOE e2 genotype [19]. We found strong association between cSS and SAE presence, and between CMBs (especially strictly lobar CMBs) and FLP presence. Our results suggest that FLP and SAE might be related to different anatomical distributions of CAA pathology, which may in part be related to underlying APOE genotype.

Our study has strengths. We included a consecutive sample of participants with lobar ICH. CT and MRI were assessed by trained blinded experienced raters with standardized rating instruments and consensus criteria with substantial or excellent intra-rater and inter-rater agreement. Moreover, MRI scans were performed soon after CT; for patients included in the SIGNaL cohort the median was 2 days (IQR 1-3).

We also acknowledge limitations. The requirement of an MRI scan and of signed informed consent could have created a selection bias towards non-severe, clinically stable ICH patients. The patients with MRI available were significantly younger, but there was not a major difference in clinical severity. We could not evaluate the accuracy of Edinburgh criteria against histopathological assessment, which is the reference standard for a diagnosis of CAA. However, histopathological analysis of brain tissue is rarely performed in clinical practice, while in clinical practice the diagnosis of CAA is often made based on the modified Boston criteria, which show good diagnostic accuracy for pathologically-proven CAA in ICH (specificity 81.2% [95% CI 61.5–92.7], sensitivity 94.7% [95% CI 82.7–98.5]) [3]. While our findings need to be validated against histopathological assessment, they

remain relevant to guide clinicians in every day clinical practice, especially where MRI is not available.

CONCLUSION

We have shown associations between putative biomarkers of parenchymal CAA (FLP and CMB), and between putative biomarkers of leptomeningeal CAA (SAE and cSS). Our findings indicate that, in lobar ICH survivors where CAA is suspected, CT biomarkers suggesting a high probability of CAA might help rule-in MRI-defined probable CAA. However, the absence of FLP and SAE on CT are probably not useful to rule-out the presence of CAA, suggesting an important continued role for MRI in the investigation of ICH survivors with suspected CAA.

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Table 1. General characteristics of the cohort

Clinical variables	**N (%)**
Age (median; IQR)	72.5 (65-78)
Female gender	81 (57.9)
Hypertension	82 (58.6)
Oral anticoagulant drug at index ICH	28 (20.0)
Prior ICH	14 (10.0)
Glasgow Coma Scale at admission (median; IQR)	15 (1)
ICH volume (median [IQR]) #	12.0 (4.5-20.0)
MRI-based variables and criteria	**N (%)**
Cerebral microbleed	
Absent	59 (42.1)
Present	81 (57.9)
1-5	37 (26.4)
6-10	14 (10.0)
11-20	14 (10.0)
>20	16 (11.4)
Lobar CMB presence	63 (45.0)
Strictly lobar CMB presence	38 (27.1)
Deep CMB presence	31 (22.1)
Brainstem CMB presence	16 (11.4)
Infratentorial CMB presence	39 (27.9)
Cortical superficial siderosis	
Absent	109 (77.9)
Present	31 (22.1)
Focal	17 (12.1)
Disseminated	14 (10.0)
Modified Boston criteria	
Non-probable CAA	86 (61.4)
Probable CAA	54 (38.6)
CT-based variables and criteria	
Finger-like projection presence	41 (29.3)
Subarachnoid extension presence	53 (37.9)
Simplified Edinburgh criteria	
Low probability of CAA	73 (52.1)
Intermediate probability of CAA	40 (28.6)
High probability of CAA	27 (19.3)

IQR, Interquartile range; ICH, intracerebral haemorrhage; CMB, cerebral microbleeds; CAA, cerebral amyloid angiopathy
 # Volume in mL; data available for 101 patients (72% of the entire cohort).

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Table 2.

Association between FLP and MRI biomarkers

	Finger-like projections		*P value*	*Agreement % (95% CI)*	*κ value (95%CI)*
	Absent	**Present**			
CMB			0.047*	54.3 (45.7 – 62.7)	0.142 (0.006 – 0.277)
Absence	47 (79.7)	12 (20.3)			
Presence	52 (64.2)	29 (35.8)			
Strictly Lobar CMB			0.014*	67.9 (59.4 - 75.5)	0.207 (0.034 – 0.380)
No	78 (76.5)	24 (23.5)			
Yes	21 (55.3)	17 (44.7)			
CMB count			0.013§	-	-
0	47 (79.7)	12 (20.3)			
0-5	28 (75.7)	9 (24.3)			
6-10	5 (35.7)	9 (64.3)			
11-20	11 (78.6)	3 (21.4)			
>20	8 (50.0)	8 (50.0)			
cSS			0.390*	64.3 (55.8 – 72.2)	0.071 (-0.097 – 0.240)
Absent	79 (72.5)	30 (27.5)			
Present	20 (64.5)	11 (35.5)			
cSS severity			0.691*	-	-
Absent	79 (72.5)	30 (27.5)			
Focal	11 (64.7)	6 (35.3)			
Disseminated	9 (64.3)	5 (35.7)			

Association between SAE and MRI biomarkers

	Subarachnoid extension		*P value*	*Agreement % (95% CI)*	*k values (95%CI)*
	Absent	**Present**			
CMB			0.815*	47.1 (38.7 – 55.8)	-0.018 (-0.0171 – 0.135)
Absence	36 (61.0)	23 (39.0)			
Presence	51 (63.0)	29 (37.0)			
Strictly Lobar CMB			0.157*	60.7 (52.1 – 68.9)	0.116 (-0.048 – 0.280)
No	67 (65.7)	35 (34.3)			
Yes	20 (52.6)	18 (47.4)			
CMB count			0.787§	-	-
0	36 (61.0)	23 (39.0)			
0-5	23 (62.2)	14 (37.8)			
6-10	7 (50.0)	7 (50.0)			
11-20	10 (71.4)	4 (28.6)			
>20	11 (68.8)	5 (31.2)			
cSS presence			0.002*	67.1 (58.7 – 74.8)	0.240 (0.081 – 0.399)
Absent	75 (68.8)	34 (31.2)			
Present	12 (38.7)	19 (61.3)			
cSS severity			0.002*	-	-
Absent	75 (68.8)	34 (31.2)			

Focal	9 (52.9)	8 (47.1)
Disseminated	3 (21.4)	11 (78.6)

FLP, finger-like projections; cSS, cortical superficial siderosis; CI, confidence interval CMB, cerebral microbleeds; SAE, subarachnoid extension; * χ^2 test*;* §Wilkoxon rank sum test

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Table 3. Comparison between simplified Edinburgh criteria and modified Boston criteria and discrimination of simplified Edinburgh criteria for Probable CAA (per MRI-based modified Boston criteria)

Classification per simplified Edinburgh criteria and modified Boston criteria: AUC = 0.62 (95%CI 0.54-0.71)

	Modified Boston criteria		
	Probable CAA	Non-probable CAA	
Simplified Edinburgh criteria			
High probability of CAA	16 (59.3)	11 (40.7)	27 (100)
Intermediate probability of CAA	18 (45.0)	22 (55.0)	40 (100)
Low probability of CAA	20 (27.4)	53 (72.6)	73 (100)

Discrimination, sensitivity, specificity, PPV and NPV of high probability of CAA (vs Intermediate/low probability) for probable CAA (per MRI-based modified Boston criteria)

	Modified Boston criteria		
	Probable CAA	Non-probable CAA	
Simplified-Edinburgh criteria			***TOTAL***
High Probability of CAA	16	11	*27*
Intermediate/low probability of CAA	38	75	*113*
TOTAL	*54*	*86*	*140*

Sensitivity	29.6% (95%CI 18.0-43.6)
Specificity	87.2% (95%CI 78.3-93.4)
PPV	59.3% (95%CI 38.8-77.6)
NPV	66.4% (95%CI 56.9-75.0)
LR+	2.3 (95%CI 1.2-4.6)
LR-	0.8 (95%CI 0.7-1.0)

CAA, cerebral amyloid angiopathy; PPV, positive predictive value; NPV, negative predictive value. LR+, positive likelihood ratio; LR-, negative likelihood ratio.

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