The Boston Criteria Version 2.0 increase the proportion of lobar intracerebral haemorrhage classified as probable cerebral amyloid angiopathy

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Cerebral amyloid angiopathy (CAA) is a common age-related small vessel disease characterised by the progressive deposition of amyloid-β in small cerebral leptomeningeal and cortical vessel walls. CAA is an important cause of lobar intracerebral haemorrhage (ICH) in older people and is important to diagnose because it has a substantially higher risk of recurrent intracerebral haemorrhage than intracerebral haemorrhage associated with arteriolosclerosis[1]. The Boston criteria - first proposed in 1995 (v1.0) and modified in 2010 (v1.5)[2] - define probable CAA by the presence of lobar intracerebral haemorrhage, cerebral microbleeds or cortical superficial siderosis, allowing non-invasive diagnosis[2]. However, their limited sensitivity led to a recent update (v2.0) incorporating non-haemorrhagic MRI markers (severe perivascular spaces in the centrum semiovale and multispot white matter hyperintensities (WMH))[3]; the clinical impact of using these criteria in practice has not been investigated.

We therefore determined the proportion of ICH reclassified as CAA using Boston criteria v2.0 compared to v1.5, in the prospective Stroke Investigation in North and Central London (SIGNAL) registry including consecutive patients admitted to the University College London Hospital hyperacute stroke service between 2nd January 2015 and 21st October 2021. Among 755 patients with ICH, we identified 217 with lobar ICH and available brain MRI. After excluding patients with ICH due to secondary causes (n=24), or without diagnostic quality MRI (n=71) we included 122 patients with lobar ICH (Table 1). MRI images were evaluated independently by three vascular neurologists; discrepancies were resolved by consensus with an expert vascular neuroradiologist (HRJ).

We found good inter-rater and intra-rater reliability for the diagnosis of probable CAA (all kappa values>0.85). Among included patients (Table 1), 36 (30%) met the criteria for probable CAA using both Boston v1.5 and v2.0. A further 11 patients (9%) were classified as probable CAA only using the Boston criteria v2.0, increasing the number of patients with probable CAA to 47 (39%) (Table 2).

Our findings indicate that the Boston criteria v2.0 substantially increases the proportion of patients with lobar ICH classified as probable CAA in comparison to the Boston criteria v1.5. Of the neuroimaging

biomarkers included in the Boston criteria v2.0, cortical superficial siderosis had the strongest association with CAA, followed by severe CSO-PVS, multiple lobar microbleeds and then the multi-spot WMH pattern. A key question is whether patients diagnosed with CAA using non-haemorrhagic markers have different, perhaps lower, risk of future ICH than those diagnosed using only traditional haemorrhagic markers, but this hypothesis requires further investigation. It will also be of interest to determine whether different neuroimaging biomarkers occur at different disease stages; we are not aware of such data in sporadic CAA, but studies of WMH and diffusion imaging microstructural alterations in Dutch-type hereditary CAA suggest that non-haemorrhagic markers may be early features of the disease, beginning approximately 10-15 years prior to the mean age of symptomatic intracerebral haemorrhage.[4]

The diagnosis of probable CAA in patients with lobar ICH who would previously have remained undiagnosed has practical implications, including the avoidance of unnecessary investigations for macrovascular causes or alternative vasculopathies (e.g., intra-arterial digital subtraction angiography or brain biopsy, both of which can cause serious complications). Diagnosing probable CAA can also provide important prognostic information for ICH recurrence[1] to guide patients, carers, and healthcare professionals.

Table 1. Clinical and magnetic resonance imaging characteristics of the cohort.

	All patients with lobar ICH (n=122)		Patients reclassified as probable CAA only using Boston criteria v2.0 (n=11)		Classified as CAA with both Boston criteria v1.5 and v2.0 (n=36)		*P* value *
Age, years	71	(58-78)	72	(64-81)	77	(71-81)	0·31
Sex							0·82
Male	62	(51%)	5	(45%)	15	(42%)	
Female	60	(49%)	6	(55%)	21	(58%)	
Race							0·59
White	77	(63%)	9	(82%)	29	(81%)	
Black	13	(11%)	0	(0%)	2	(5%)	
Asian	7	(6%)	0	(0%)	1	(3%)	
Other	25	(20%)	2	(18%)	4	(11%)	
Hypertension	69	(57%)	6	(55%)	19	(53%)	0·92
Diabetes	12	(10%)	0	(0%)	3	(8%)	0·20
Atrial fibrillation	14	(11%)	2	(18%)	5	(14%)	0·73
Heart failure	3	(2%)	0	(0%)	1	(3%)	0·46
Previous stroke/TIA	23	(19%)	2	(18%)	10	(28%)	0·51
NIHSS	3	(1-9)	2	(0-9)	3	(0-5)	0·99
Baseline mRS	0	(0-1)	0	(0-1)	1	(0-1)	0·07
Discharge mRS	3	(2-4)	3	(1-4)	3	(2-4)	0·89
Haemorrhage volume, ml	10·5	(4·1-25·1)	7.8	(6·3-13·0)	6·9	(3·2-15·5)	0·35
Intraventricular haemorrhage	27	(22%)	1	(9%)	6	(17%)	0·52
CMB							
Lobar CMB presence	76	(62%)	0	(0%)	32	(89%)	<0·001
0	46	(38%)	11	(100%)	4	(11%)	
1-5	41	(33%)	0	(0%)	19	(53%)	<0·001
>=6	35	(29%)	0	(0%)	13	(36%)	
Deep CMB presence	46	(38%)	0	(0%)	0	(0%)	NA
0	76	(62%)	11	(100%)	36	(100%)	
1-5	38	(31%)	0	(0%)	0	(0%)	NA
>6	8	(7%)	0	(0%)	0	(0%)	
Infratentorial CMB presence	42	(34%)	1	(9%)	7	(19%)	0·40
0	80	(66%)	10	(91%)	29	(80%)	
1-5	34	(28%)	1	(9%)	6	(17%)	0·61
>6	8	(6%)	0	(0%)	1	(3%)	
Total CMB presence	89	(73%)	1	(9%)	32	(89%)	<0·001
0	33	(27%)	10	(91%)	4	(12%)	
1-5	40	(33%)	1	(9%)	16	(44%)	<0·001
>6	49	(40%)	0	(0%)	16	(44%)	
Cortical superficial siderosis	30	(25%)	0	(0%)	21	(58%)	<0·001
Disseminated cortical superficial siderosis	12	(10%)	0	(0%)	10	(28%)	0·01

Enlarged perivascular space	119	(98%)	10	(91%)	35	(97%)	0·40
Severe perivascular space in centrum semiovale	53	(43%)	7	(64%)	24	(67%)	0·50
WMH	112	(92%)	10	(91%)	35	(97%)	0·40
Moderate to severe WMH	90	(74%)	6	(55%)	31	(86%)	0·03
Multispot WMH pattern	49	(40%)	6	(55%)	22	(63%)	0·62

Data are presented as median (IQR) for continuous variables and n (%) for categorical variables. CAA = cerebral amyloid angiopathy. TIA = transient ischaemic attack. NIHSS = national institutes of health stroke scale. mRS = modified Rankin score. MRI = magnetic resonance imaging. CMB = cerebral microbleeds. WMH = white matter hyperintensities.

* The difference between reclassified CAA and non-reclassified CAA groups was assessed using the Wilcoxon rank sum test for continuous variables and the Chi-square test for categorical variables.

Table 2. Reclassification of probable CAA according to the presence of new MRI features in the Boston criteria v2.0.

MRI features	**Number of patients with each MRI feature reclassified as probable CAA using the Boston criteria v2.0 (total n=11)**	
Severe CS-PVS	5	(46%)
Multispot WMH pattern	4	(36%)
Severe CS-PVS and multispot WMH pattern	2	(18%)
Convexity subarachnoid haemorrhage	0	(0%)

Data are presented as n (%) for categorical variables. CAA = cerebral amyloid angiopathy. CS-PVS = centrum semiovale perivascular space. MRI = magnetic resonance imaging.

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References

1. Charidimou A, Imaizumi T, Moulin S, et al. Brain hemorrhage recurrence, small vessel disease type, and cerebral microbleeds: A meta-analysis. *Neurology* 2017; **89**(8): 820-9.
2. Charidimou A, Frosch MP, Al-Shahi Salman R, et al. Advancing diagnostic criteria for sporadic cerebral amyloid angiopathy: Study protocol for a multicenter MRI-pathology validation of Boston criteria v2.0. *Int J Stroke* 2019; **14**(9): 956-71.
3. Charidimou A, Boulouis G, Frosch MP, et al. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. *Lancet Neurol* 2022; **21**(8): 714-25.
4. Shirzadi Z, Yau WW, Schultz SA, et al. Progressive White Matter Injury in Preclinical Dutch Cerebral Amyloid Angiopathy. *Ann Neurol* 2022; **92**(3): 358-63.