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Acute ischaemic brain lesions in intracerebral haemorrhage: multicentre cross-sectional magnetic resonance imaging study

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Subclinical acute ischaemic lesions on brain magnetic resonance imaging have recently been described in spontaneous intracerebral haemorrhage, and may be important to understand pathophysiology and guide treatment. The underlying mechanisms are uncertain. We tested the hypothesis that ischaemic lesions are related to magnetic resonance imaging markers of the severity and type of small-vessel disease (hypertensive arteriopathy or cerebral amyloid angiopathy) in a multicentre, cross-sectional study. We studied consecutive patients with intracerebral haemorrhage from four specialist stroke centres, and age-matched stroke service referrals without intracerebral haemorrhage. Acute ischaemic lesions were assessed on magnetic resonance imaging (<3 months after intracerebral haemorrhage) using diffusion-weighted imaging. White matter changes and cerebral microbleeds were rated with validated scales. We investigated associations between diffusion-weighted imaging lesions, clinical and radiological characteristics. We included 114 patients with intracerebral haemorrhage (39 with clinically probable cerebral amyloid angiopathy) and 47 age-matched controls. The prevalence of diffusion-weighted imaging lesions was 9/39 (23%) in probable cerebral amyloid angiopathy-related intracerebral haemorrhage versus 6/75 (8%) in the remaining patients with intracerebral haemorrhage (P = 0.024); no diffusion-weighted imaging lesions were found in controls. Diffusion-weighted imaging lesions were mainly cortical and were associated with mean white matter change score (odds ratio 1.14 per unit increase, 95% confidence interval 1.02–1.28, P = 0.024) and the presence of strictly lobar cerebral microbleeds (odds ratio 3.85, 95% confidence interval 1.15–12.93, P = 0.029). Acute, subclinical ischaemic brain lesions are frequent but previously underestimated after intracerebral haemorrhage, and are three times more common in cerebral amyloid angiopathy-related intracerebral haemorrhage than in other intracerebral haemorrhage types. Ischaemic brain lesions are associated with white

matter changes and cerebral microbleeds, suggesting that they result from an occlusive small-vessel arteriopathy. Diffusion-weighted imaging lesions contribute to the overall burden of vascular-related brain damage in intracerebral haemorrhage, and may be a useful surrogate marker of ongoing ischaemic injury from small-vessel damage.

Introduction

Intracerebral haemorrhage is the most disabling form of stroke, for which acute treatments are limited and there is an urgent need to better understand the pathophysiology to help enhance the development of new treatments. Most intracerebral haemorrhages (>75%) are classified as primary (spontaneous), due to rupture of small arteries of the brain, affected by two main disease processes: hypertensive arteriopathy and cerebral amyloid angiopathy (CAA). Hypertensive arteriopathy, characterized by lipohyalinosis and fibrinoid necrosis of small deep perforating arteries, is an important cause of intracerebral haemorrhage, particularly in deep brain structures, including the basal ganglia, brainstem and thalamus. CAA is defined by amyloid-β deposition in the media and adventitia of cortical and leptomeningeal small- to medium-sized arteries, arterioles and capillaries (Vinters, 1987; Attems, 2005) and is considered an important cause of lobar intracerebral haemorrhage, especially in the elderly.

Diffusion-weighted imaging (DWI) detects acute brain ischaemia with sensitivity approaching 100% (Davis et al., 2006). Recent studies using DWI have detected clinically unsuspected areas of acute ischaemia in intracerebral haemorrhage (Kimberly et al., 2009; Menon et al., 2009; Prabhakaran et al., 2010), but the mechanisms underlying these lesions are not clear. Ischaemia could, for instance, be due to an active occlusive small-vessel arteriopathy (e.g. CAA); or due to cerebral hypoperfusion due to reduced blood pressure in the context of a failure of autoregulation. It is of practical importance to establish the underlying mechanism because one of the few promising treatments currently under investigation for intracerebral haemorrhage is aggressive blood pressure lowering to reduce haematoma expansion (Anderson et al., 2008; Delcourt et al., 2010). We reasoned that if ischaemic DWI lesions in intracerebral haemorrhage are due to occlusive small-vessel damage, then they should be related to the severity of the underlying small-vessel disease. We tested this hypothesis using MRI to detect acute ischaemic brain lesions and relating them to two MRI markers of cerebral small-vessel disease: white matter changes and cerebral microbleeds. Since neuropathological analyses have identified asymptomatic ischaemic infarction as a common finding in the brain of patients with advanced CAA (Okazaki et al., 1979; Olichney et al., 1995; Cadavid et al., 2000; Haglund et al., 2006; Soontornniyomkij et al., 2010), we also hypothesized that ischaemic lesions would be most common in intracerebral haemorrhage attributed to probable CAA, and in association with strictly lobar cerebral microbleeds, a radiological marker for CAA.

Materials and methods

Participants

We included patients within 3 months of spontaneous intracerebral haemorrhage consecutively referred to four specialist stroke centres in the United Kingdom and Belgium. The hospitals were: The National Hospital for Neurology and Neurosurgery, Queen Square (London), Addenbrooke's Hospital (Cambridge), Cliniques Universitaires Saint Luc (Brussels) and Cliniques Universitaires UCL de Mont Godinne (Yvoir). All centres have a policy of routine MRI for investigating the cause of spontaneous intracerebral haemorrhage. We identified all cases with spontaneous lobar intracerebral haemorrhage and appropriate MRI data available. Probable CAA was defined according to the Boston criteria: patients with two or more spontaneous strictly lobar intracerebral haemorrhage over the age of 55 years, without any other identified cause (Knudsen et al., 2001). The remaining patients with spontaneous intracerebral haemorrhage not fulfilling the criteria for CAA [e.g. one strictly lobar haemorrhage, mixed (deep and lobar) haemorrhages and strictly deep haemorrhage(s)] were classified as non-CAA related. All cases were ascertained using overlapping methods from prospective clinical databases and radiological reports. Clinical information (demographics, vascular risk factors, use of anti-thrombotics) was obtained from prospective databases and medical records. A total of 422 patients with intracerebral haemorrhage were screened, of whom 129 were excluded because of diagnosis of non-spontaneous intracerebral haemorrhage (e.g. secondary to haemorrhagic infarction, aneurysms, tumours, cavernomas, arteriovenous malformations, coagulation disorders or use of oral anti-coagulants, venous thrombosis or head injuries), and 179 because MRI with the necessary sequences of adequate quality was not available within 3 months of the acute intracerebral haemorrhage.

Age-matched controls were ascertained from a database of consecutive patients with suspected stroke attending the neurovascular clinic at The National Hospital for Neurology and Neurosurgery but with a final non-stroke/transient ischaemic attack diagnosis for their presenting symptoms after full investigation. They were matched for age with the CAA-related patients with intracerebral haemorrhage using an unbiased group-matching process blinded to their final diagnoses and imaging findings.

The study received ethical approval by the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee, the Commission d'Ethique Biomédicale Hospitalo Facultaire of the Faculté de Médicine (Université Catholique de Louvain), and the Comité d'éthique médicale of the Cliniques Universitaires UCL de Mont Godinne.

Magnetic resonance imaging protocols

The MRI stroke protocol was standardized in each hospital. Imaging was at 1.5T field strength for the majority of patients (105/114, 92%)

and included T$_1$-weighted, T$_2$-weighted, fluid attenuation inversion recovery (FLAIR), DWI and gradient-recalled echo T$_2$* sequences.

National Hospital for Neurology and Neurosurgery, Queen Square

MRIs were carried at 1.5T field strength. Axial gradient-recalled echo T$_2$* images were obtained using a General Electric Genesis Signa Scanner (GE Medical Systems) [repetition time 300 ms, echo time 40 ms, flip angle 20°, field of view 24 × 18, matrix 256 × 160, slice thickness 5 mm, gap 1.5 mm, NEX (number of excitations) 1] for 38 patients. Four patients were scanned on a Siemens Avanto Scanner (repetition time 800 ms, echo time 26 ms, flip angle 20°, field of view 24 × 18, matrix 512 × 448, slice thickness 5 mm, slice gap 1.5 mm, NEX 1). Axial DWI sequences were acquired using the following parameters: repetition time 1000 ms, echo time 98.5 ms, $b = 0/1000$ s/mm^2, slice thickness 5 mm, gap 0.5 mm, field of view 250 mm, matrix 256 × 256 (GE); repetition time 3200 ms, echo time 78 ms, slice thickness 5 mm, gap 1.5 mm; field of view 250 mm, matrix 256 × 256 (Siemens).

Addenbrooke's Hospital, Cambridge

Twelve patients were scanned on a 1.5T GE Medical Systems Signa Excite scanner. Gradient-recalled echo T$_2$* sequences were obtained in the axial plane using the following parameters: repetition time 460–660 ms, echo time 15 ms, field of view 22 cm, matrix 256 × 192–224, slice thickness 6 mm, gap 7 mm, NEX 2. Four patients were scanned on a 3T GE Medical Systems Signa HDX scanner, with gradient-recalled echo parameters as follows: repetition time 600 ms, echo time 15 ms, field of view 22 cm, matrix 256 × 192, slice thickness 6 mm, gap 7 mm. Axial DWI sequences were acquired with the following parameters: at 1.5T, repetition time 10 000 ms, echo time 61.6 ms, $b = 0/1000$ s/mm^2, slice thickness 5 mm, no gap, field of view 280 mm; at 3T, repetition time 6000 ms, echo time 61.6 ms.

Cliniques Universitaires Saint Luc, Brussels

At St Luc, axial gradient-recalled echo T$_2$* sequences were acquired, with parameters as follows: 3T, repetition time 230 ms, echo time 16 ms, slice thickness 4 mm, gap 0.4 mm; 1.5T, repetition time 230–240 ms, echo time 50–70 ms, slice thickness 5 mm, gap 1 mm. Axial DWI was acquired using the following parameters: repetition time 4500 ms, echo time 94 ms, $b = 0/1000$ s/mm^2, slice thickness 5 mm, gap 0.5 mm; field of view 240 mm^2, matrix 256 × 256; repetition time 3312 ms, echo time 93 ms, $b = 0/1000$ s/mm^2, slice thickness 5 mm, gap 1 mm, in-plane resolution 1.88 × 2.33 mm^2 reconstructed to 0.94 mm^2; and repetition time 2907 ms, echo time 55 ms, flip angle 90°, $b = 0/1000$ s/mm^2, slice thickness 4 mm, gap 0.4 mm, in-plane resolution 1.8 × 2.27 mm^2 reconstructed to 0.9 mm^2.

Cliniques Universitaires UCL de Mont Godinne

All MRIs were carried at 1.5T field strength. Gradient-recalled echo T$_2$* sequences were obtained in the axial plane on a Siemens Magnetom Symphony System [repetition time 921 ms, echo time 22 ms, field of view 230 mm, matrix 256 (1.2 × 0.9 × 0.4 mm), slice thickness 4 mm, slice gap 10%]; and an echo planar imaging sequence: repetition time 4750 ms, echo time 46 ms, field of view 250, matrix 128 (2 × 2 × 3 mm), slice thickness 3 mm, slice gap 10%. Axial DWI sequences were acquired with the following parameters: repetition time 4900 ms, echo time 93 ms, $b = 0/1000$ s/mm^2, slice thickness 4 mm, gap 0.4 mm, field of view 250 mm, matrix 256 × 256.

Image analysis

All images were analysed by a clinical neurologist (S.M.G.), blinded to clinical information. Acute ischaemic lesions were identified as bright areas on DWI sequences and corresponding dark areas on apparent diffusion coefficient maps by S.M.G. and reviewed by a senior vascular neuroradiologist (H.R.J.) to reach consensus, blinded to other imaging sequences and clinical details. DWI lesions in close proximity (<20 mm) to an intracerebral haemorrhage were excluded. The locations of DWI lesions were classified as cortical or cortical–subcortical (including cerebellum) or deep (including brainstem). We recorded the presence and measured the number of acute symptomatic intracerebral haemorrhages and the median total number of intracerebral haemorrhage on MRI. Intracerebral haemorrhage distribution was classified as lobar (including cerebellum) and deep (including brainstem). S.M.G. rated the presence, number and distribution of cerebral microbleeds on gradient-recalled echo T$_2$* images using the microbleed anatomical rating scale (MARS) (Gregoire *et al.*, 2009). White matter changes (WMC) were rated on a 4-point scale, with scores ranging from 0 to 3 (Wahlund *et al.*, 2001) on sagittal T$_1$, coronal fluid attenuation inversion recovery and axial T$_2$-weighted magnetic resonance images. The presence of subarachnoid blood, intraventricular haemorrhage and superficial siderosis were also recorded.

Statistical analysis

We compared the characteristics of patients with probable CAA-related intracerebral haemorrhage and the remaining patients with spontaneous intracerebral haemorrhage. Population characteristics were compared using the chi-square test and Fisher's exact test for categorical variables. Continuous variables were analysed using independent-samples t-test (when the data distribution was normal) and the Mann–Whitney U-tests (when the distribution was non-normal). We used univariate binary logistic regression to test for the factors associated with DWI lesions. The threshold of statistical significance was set at $P < 0.05$ for all analyses.
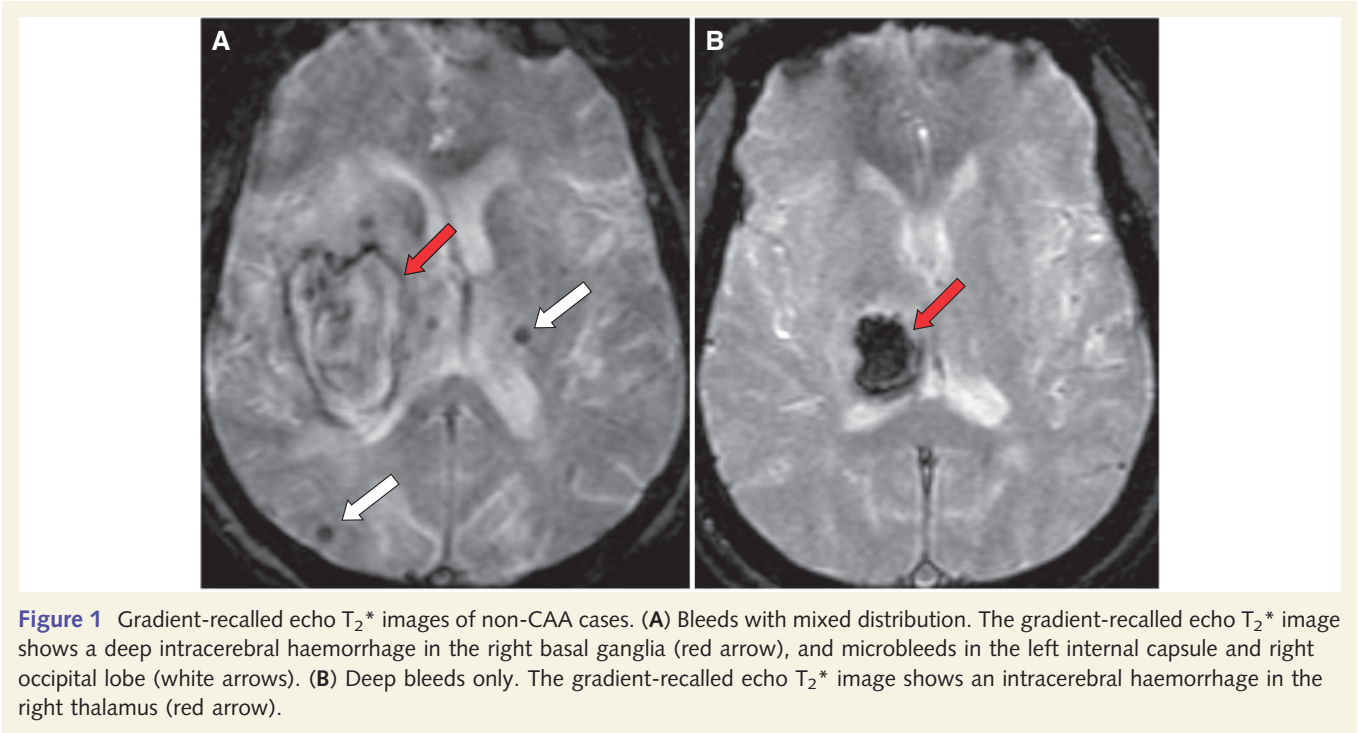
Results

The final cohort consisted of 114 patients with intracerebral haemorrhage, 39 of whom fulfilled the criteria for probable CAA; and 47 age-matched controls. The clinical and radiological characteristics of the intracerebral haemorrhage cohort are reported in Table 1. The patients with intracerebral haemorrhage excluded from the study were not significantly different from those included in measures of intracerebral haemorrhage severity including: median intracerebral haemorrhage volume 17.7 cm^3 (range 0.40–73.56 cm^3) in patients excluded versus 10.5 cm^3 (range 0.31–50.00 cm^3) in patients included, $P = 0.93$; median Glasgow Coma Score on admission: 14 (range 9–15) in patients excluded versus 15 (range 6–15) in patients included, $P = 0.691$. Patients excluded had a higher prevalence of symptomatic lobar intracerebral haemorrhage (excluded: 82% lobar versus included 54% lobar, $P = 0.002$).

In our age-matched control group, the following prevalences of vascular risk factors were found: hypertension 83%, diabetes 13%, previous history of stroke 29% and use of anti-thrombotics 46%. Controls had the following final diagnoses: syncope [$n = 7$ (17%)]; vestibular disturbance [$n = 7$ (15%)]; asymptomatic

Table 1 Characteristics of patients with probable CAA compared with patients with other causes of spontaneous intracerebral haemorrhage

Clinical and radiological characteristics of the patients	Probable CAA (n = 39)	All other intracerebral haemorrhage[a] (n = 75)	P-value
Clinical demographics			
Age, median (range) (years)	74 (49–90)	69 (49–93)	0.094
Sex, female (%)	14 (36)	30 (40)	0.669
Hypertension (%)	24 (62)	64 (85)	0.013*
Smoking history (%)	11 (28)	23 (31)	0.884
Diabetes (%)	6 (15)	13 (17)	0.859
Statins on admission (%)	8 (21)	16 (21)	1.000
Previous history of ischaemic stroke or transient ischaemic attack (%)	5 (13)	7 (9)	0.549
On anti-thrombotics (%)	11 (28)	26 (35)	0.537
First ever intracerebral haemorrhage (%)	20 (51)	61 (81)	<0.001**
Interval between intracerebral haemorrhage and MRI, median (range) (days)	8 (0–76)	5 (0–84)	0.300
Radiological characteristics			
Total score of white matter change, median (range)	9 (2–26)	9 (0–20)	0.505
Presence of cortical infarcts (%)	2 (5)	4 (5)	1.000
Presence of lacunar infarcts (%)	9 (23)	21 (28)	0.284
Presence of microbleeds (%)	35 (90)	42 (56)	<0.001**
Presence of multiple intracerebral haemorrhage (%)	19 (49)	14 (19)	<0.001**
Total number of intracerebral haemorrhage on MRI, median (range)	1 (0–5)	1 (1–3)	0.002**
Presence of subarachnoid or intraventricular haemorrhage (%)	15 (38)	11 (15)	0.004**

a Possible CAA and non-CAA.
*$P < 0.05$; **$P < 0.01$.

Figure 1 Gradient-recalled echo T_2* images of non-CAA cases. (**A**) Bleeds with mixed distribution. The gradient-recalled echo T_2* image shows a deep intracerebral haemorrhage in the right basal ganglia (red arrow), and microbleeds in the left internal capsule and right occipital lobe (white arrows). (**B**) Deep bleeds only. The gradient-recalled echo T_2* image shows an intracerebral haemorrhage in the right thalamus (red arrow).

carotid stenosis [$n = 6$ (13%)]; transient global amnesia [$n = 4$ (9%)]; functional [$n = 4$ (9%)]; small-vessel disease without acute stroke [$n = 4$ (9%)]; migraine [$n = 4$ (9%)]; memory problems [$n = 2$ (4%)]; incidental cerebral infarction [$n = 1$ (2%)]; and other [$n = 7$ (15%)].

Examples of gradient-recalled echo T_2* MRI studies of two non-CAA patients are shown in Fig. 1: one with a mixed distribution of haemorrhages (a large deep symptomatic haemorrhage with both deep and lobar cerebral microbleeds); and one with exclusively deep haemorrhages. There were 33 patients with

multiple ($\geqslant 2$) intracerebral haemorrhages (29%). In these, all intracerebral haemorrhages identified on MRI (apart from the symptomatic lesion) occurred at previous remote times, except in two patients with simultaneous multiple intracerebral haemorrhages at presentation.

Prevalence of diffusion-weighted imaging lesions

The prevalence of patients with DWI lesions was as follows: intracerebral haemorrhage overall = 15/114 (13%); probable CAA = 9/39 (23%); all other intracerebral haemorrhage = 6/75

(8%); and controls = 0/47 (0%). Two patients had two DWI lesions; the rest had a single DWI lesion. Representative examples of DWI lesions are shown in Fig. 2. DWI lesions were more common in patients with probable CAA compared with patients with other causes of intracerebral haemorrhage ($P = 0.024$). DWI lesions were most commonly found in lobar cortical–subcortical areas [$n = 12$ (75%)], especially the frontal lobes [$n = 6$ (38%)]. DWI lesions were all round or ovoid; their size was 0.42–1.46 cm diameter in patients with probable CAA, and 0.25–1.50 cm in patients with other causes of spontaneous intracerebral haemorrhage ($P = 0.328$). Half of the MRI scans were done within 1 week of the presenting intracerebral haemorrhage [63/114 (55%)]; and
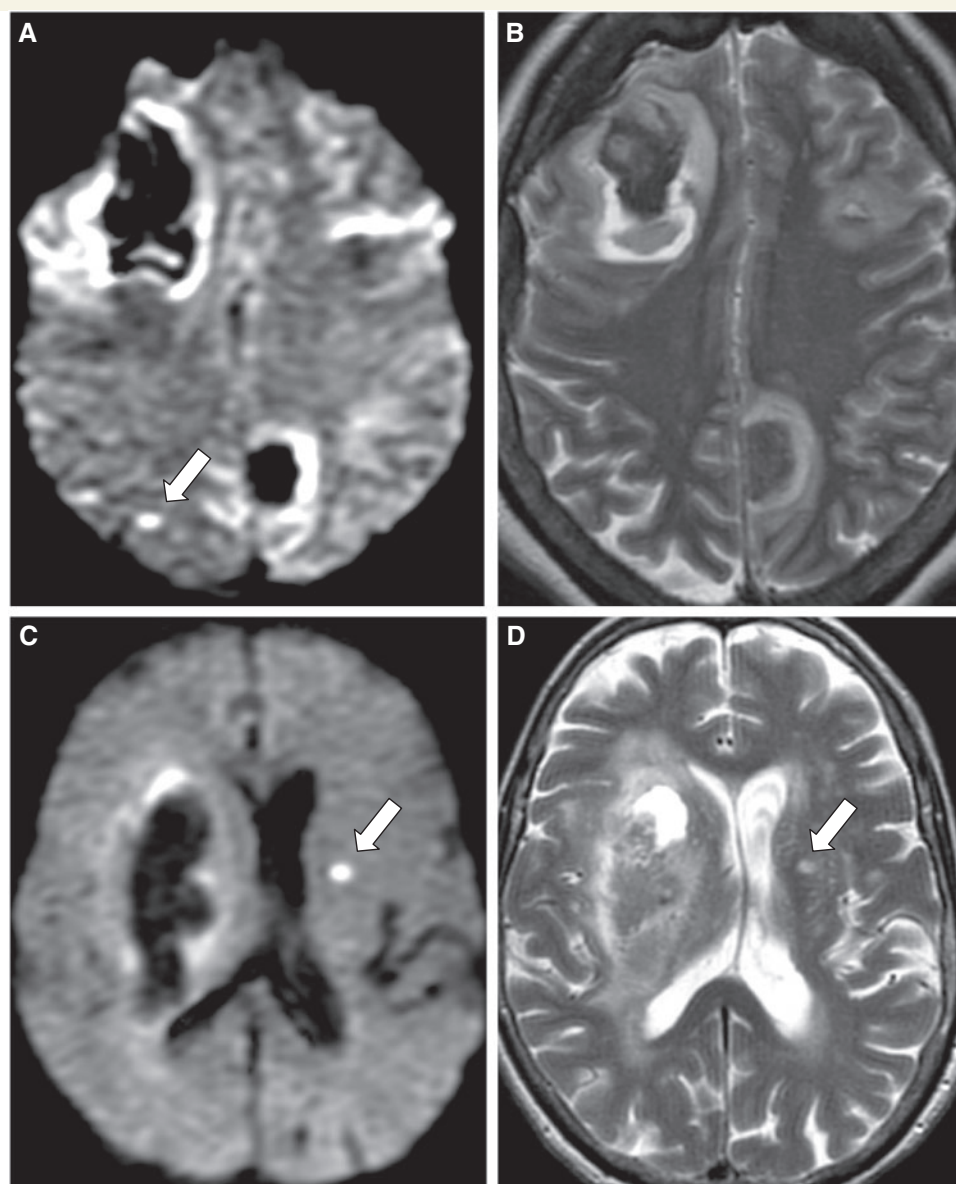

Figure 2 Examples of positive DWI lesions. (**A** and **B**) Probable CAA-related intracerebral haemorrhage. (**A**) DWI sequence showing presence of small ischaemic lesion in the right parietal lobe (white arrow) in the presence of two lobar intracerebral haemorrhage, frontal and parietal, suggestive of CAA; (**B**) corresponding T_2-weighted sequence. (**C** and **D**) Non-CAA-related intracerebral haemorrhage. (**C**) DWI sequence showing presence of small lacunar ischaemic lesion in the left lentiform nucleus (white arrow) in the presence of deep intracerebral haemorrhage; (**D**) a small infarct is visible on the corresponding T_2-weighted sequence (white arrow).

99/114 (87%) within 1 month. The longest interval between presenting intracerebral haemorrhage and MRI was 84 days. About one-third of DWI lesions were detected within 1 week [6/17 (35%)]; 14/17 (82%) were detected within 1 month. The latest DWI lesion detected was at 64 days after the presenting intracerebral haemorrhage. No DWI lesions were associated with any new clinical symptoms.

Patients with DWI lesions had more severe white matter change [mean total score 12 (range 3–17) versus 8 (range 0–26), $P = 0.007$], and a higher prevalence of lobar cerebral microbleeds [14/15 (93%) versus 57/99 (58%), $P = 0.008$], but not deep cerebral microbleeds [4/15 (27%) versus 28/99 (28%)] (Table 2). There was no difference in admission systolic or diastolic blood pressure between patients with and without DWI lesions.

Estimated incidence of diffusion-weighted imaging lesions

Assuming that DWI lesions remain detectable for ~10 days after stroke (Burdette et al., 1998), then the estimated annual incidence can be calculated as:

$$[\text{Total number of DWI lesions/number of patients}] \times$$
$$[365 \text{ (days per year)/duration of DWI lesions (days)}]$$

For a consistent incidence of DWI lesions per year, the estimated annual incidence in the whole cohort of patients with intracerebral haemorrhage is therefore $(17/114) \times (365/10) = 5.1$ silent

infarctions per person-year; in probable CAA-related intracerebral haemorrhage the estimated annual incidence is $(9/39) \times (365/10) = 8.4$ silent infarctions per person-year.

Factors associated with diffusion-weighted imaging lesions

In univariate regression analysis, significant predictors of DWI lesions were smoking history, diagnosis of probable CAA, total score of white matter change, and the presence of strictly lobar cerebral microbleeds (Table 3). In multivariate analysis, DWI lesions were associated with both mean white matter change score [odds ratio (OR) 1.14 per unit increase, 95% confidence interval (CI) 1.02–1.28, $P = 0.024$] and the presence of strictly lobar cerebral microbleeds (OR 3.85, 95% CI 1.15–12.93, $P = 0.029$) (Table 4). These associations remained significant after adjustment for age and gender. Adjusting the analysis for variation in magnetic field strength (1.5 or 3T) did not substantially weaken the association between strictly lobar microbleeds and the presence of DWI lesions (adjusted OR 3.73, 95% CI 1.11–12.57, $P = 0.034$).

There was no statistically significant difference in the median intracerebral haemorrhage volume between DWI-positive and DWI-negative groups. For DWI-negative patients, median intracerebral haemorrhage volume was 10.25 cm^3 (range 0.31–37.63 cm^3), while in DWI-positive patients, median intracerebral

Table 2 Characteristics of patients with and without DWI lesions

Clinical and radiological characteristics of the patients	DWI (+) lesion (n = 15)	DWI (−) lesion (n = 99)	P-value
Clinical demographics			
Age, median (range) (years)	73 (49–88)	71 (19–93)	0.973
Sex, female (%)	4 (27)	10 (10)	0.308
Hypertension (%)	10 (67)	78 (80)	0.307
Interval between intracerebral haemorrhage and MRI, median (range) (days)	10 (0–64)	4 (0–84)	0.471
Systolic blood pressure, mean (SD) (mmHg)	162 (37)	161 (29)	0.840
Diastolic blood pressure, mean (SD) (mmHg)	85 (21)	87 (16)	0.693
Smoking history (%)	8 (53)	26 (27)	0.067
Diabetes (%)	4 (27)	15 (16)	0.284
Statins on admission (%)	4 (27)	20 (21)	0.736
Previous history of ischaemia or transient ischaemic attack (%)	3 (20)	9 (9)	0.202
On anti-thrombotics (%)	3 (20)	34 (36)	0.229
Diagnosis of probable CAA (%)	9 (60)	30 (30)	0.024*
Radiological characteristics			
Total score of white matter change, median (range)	12 (3–17)	8 (0–26)	0.007**
Presence of cortical infarcts (%)	0 (0)	6 (6)	1.000
Presence of lacunar infarcts (%)	4 (27)	26 (26)	0.353
Presence of multiple intracerebral haemorrhage (%)	5 (33)	28 (29)	0.764
Total number of intracerebral haemorrhage on MRI, median (range)	1 (1–3)	1 (0–5)	0.581
Presence of subarachnoid or intraventricular haemorrhage (%)	5 (33)	21 (21)	0.327
Presence of strictly lobar microbleeds including cerebellum (%)	14 (93)	57 (58)	0.008**
Presence of deep microbleeds including brainstem (%)	4 (27)	28 (28)	1.000
Total number of strictly lobar microbleeds, median (range)	4 (0–14)	1 (0–294)	0.028*
Total number of deep microbleeds, median (range)	0 (0–14)	1 (0–14)	0.983

*$P < 0.05$; **$P < 0.01$.

Table 3 Univariate regression analysis testing the factors associated with DWI lesions

Factors associated with DWI lesions	OR (95% CI)	*P*-value
Clinical characteristics		
Age (years)	1.00 (0.96–1.05)	0.941
Sex, male	0.54 (0.16–1.80)	0.314
Hypertension	0.49 (0.15–1.59)	0.234
Number of blood pressure medications at time of intracerebral haemorrhage	0.88 (0.51–1.53)	0.648
Smoking history	3.08 (1.01–9.33)	0.047*
Diabetes	1.96 (0.55–6.99)	0.298
High cholesterol	0.77 (0.39–1.49)	0.438
On anti-thrombotics	0.45 (0.12–1.70)	0.238
Classification of intracerebral haemorrhage mechanism		
Diagnosis of probable CAA	3.45 (1.13–10.56)	0.030*
Radiological characteristics		
Total score of white matter change	1.13 (1.02–1.26)	0.019*
Presence of multiple intracerebral haemorrhage	1.23 (0.39–3.93)	0.724
Presence of lacunar infarcts	4.46 (0.47–42.5)	0.194
Presence of microbleeds		
Presence of microbleeds	8.00 (1.01–63.38)	0.049*
Presence of strictly lobar microbleeds, including cerebellum	10.32 (1.31–81.55)	0.027*
Presence of deep microbleeds, including brainstem	0.92 (0.27–3.14)	0.897

*$P < 0.05$.

Table 4 Multivariate regression analysis showing the factors associated with DWI lesions

Factors associated with DWI lesions	OR (95% CI)	*P*-value
Mean white matter change score	1.14 (1.02–1.28)	0.024
Strictly lobar microbleeds	3.85 (1.15–12.93)	0.029
Age (years)	0.97 (0.92–1.03)	0.374
Sex	0.62 (0.17–2.29)	0.469

haemorrhage volume was $12.09\,cm^3$ (range $0.58–50.00\,cm^3$) ($P = 0.892$).

Discussion

In this study, we frequently detected subclinical acute ischaemic brain lesions in patients with intracerebral haemorrhage; they were about three times more common in probable CAA-related intracerebral haemorrhage compared with the other cases of intracerebral haemorrhage. We found no DWI-hyperintense lesions in our age-matched controls despite them having a similar or higher prevalence of conventional vascular risk factors to the patients with intracerebral haemorrhage. DWI lesions were associated with markers of small-vessel damage including total white matter change and the presence of lobar cerebral microbleed, but not with admission blood pressure.

Overall, DWI-positive lesions were predominately located in lobar areas, mainly in the cortical–subcortical areas of the frontal and temporal lobes. They were small and mostly ovoid or round in shape. The distribution and morphology of the detected DWI lesions correlates well with the 'microinfarcts' identified in neuropathological studies of patients with CAA (Okazaki *et al.*, 1979; Cadavid *et al.*, 2000; Haglund *et al.*, 2006). Since these lesions were associated with markers of small-vessel damage severity (white matter change and cerebral microbleeds), rather than conventional risk factors, they probably represent acute small-vessel infarcts related to small-vessel arteriopathy, especially CAA. About a third of silent ischaemic lesions were detected within 1 week after intracerebral haemorrhage, and ~80% of them within 1 month, which suggests a possible early peak followed by a descending incidence over time, but we were unable to investigate this further as we did not acquire repeat imaging studies in this cohort.

To our knowledge, only one imaging study has investigated the presence of silent ischaemic lesions in CAA (Kimberly *et al.*, 2009); DWI-hyperintense lesions were identified in 12 out of 78 subjects (15%) with probable or definite CAA, while no lesions were found in a control group of 55 subjects with Alzheimer's disease or mild cognitive impairment ($P = 0.001$). In agreement with our findings, the authors did not find an association between DWI lesions and conventional risk factors. In contrast to our results, they found no association between DWI lesions and white matter change, but this study did not include any intracerebral haemorrhage cases not attributed to CAA, and therefore was not representative of the full spectrum of spontaneous intracerebral haemorrhage. Another recent study found DWI lesions in 23% of patients in a cohort of 118 patients with intracerebral haemorrhage scanned within 1 month, and found that DWI lesions were associated with aggressive blood pressure lowering (Prabhakaran *et al.*, 2010), but this study did not investigate the relationship of DWI lesions to MRI markers of small-vessel disease and did not use formal criteria to define CAA.

What are the implications of our findings on the understanding of intracerebral haemorrhage pathophysiology? We demonstrated a high prevalence of silent acute ischaemic events within the first 3 months after CAA-related intracerebral haemorrhage at a mean time of 8 days. More than 80% of the lesions occurred within 1 month post-intracerebral haemorrhage. Since DWI lesions are positive only for ~10 days (Burdette *et al.*, 1998) and were still detectable in our study up to ~2 months (Table 2), these lesions are likely to be a dynamic persisting phenomenon in patients with intracerebral haemorrhage, and a common feature of the underlying arteriopathy. Ischaemia may therefore be a previously unrecognized cause of progressive disability with possible relevance for clinical outcome after intracerebral haemorrhage. The lack of association with admission blood pressure suggests that hypoperfusion resulting from low systemic blood pressure is unlikely to have caused these ischaemic lesions, although we do not have detailed information on blood pressure control. Imaging data suggest that autoregulation is largely preserved in acute intracerebral haemorrhage, supporting this conclusion (Reinhard *et al.*, 2010).
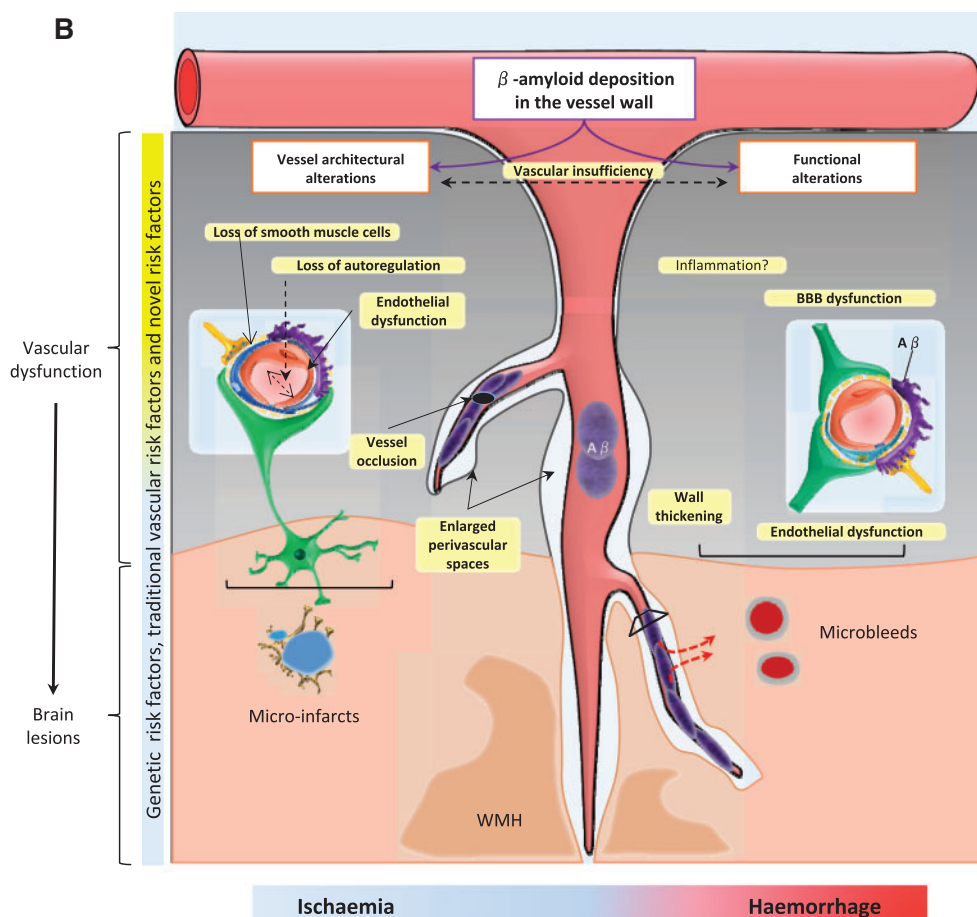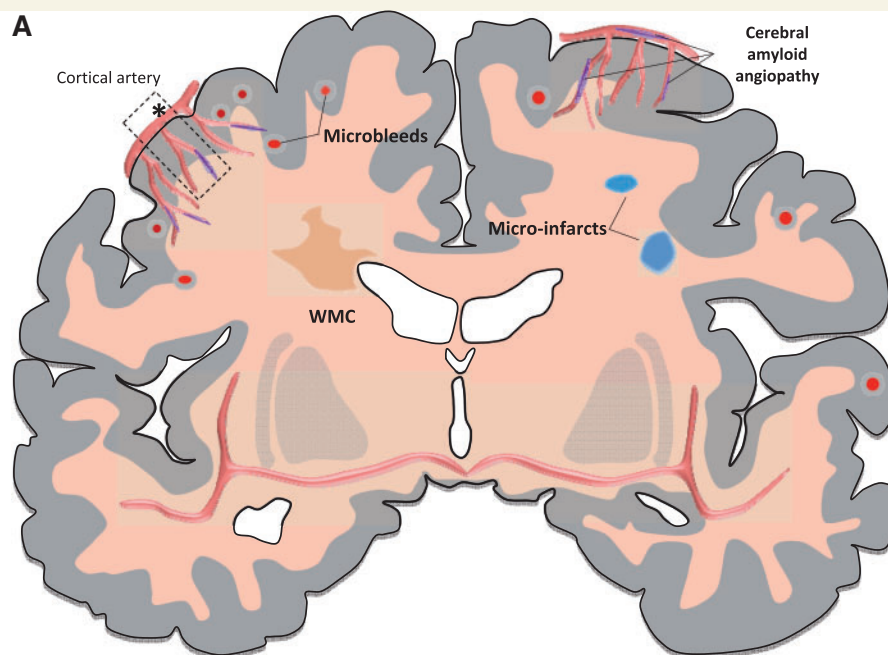
Artwork: Dr A Charidimou

Figure 3 Schematic diagram of microvascular effects of CAA and possible underlying pathophysiological pathways. (**A**) The different brain lesions associated with small-vessel disease in patients with sporadic CAA. CAA preferentially affects the small arteries and arterioles of the cerebral cortex and grey-white matter junction by the deposition of amyloid-β in the vessel walls (purple). CAA is associated with cerebral microbleeds in a mainly cortical distribution and with white matter changes (WMC). Micro-infarcts appearing as DWI-positive

(continued)

Indeed, lowering blood pressure is one of the most promising available treatments in acute intracerebral haemorrhage, having been shown to reduce haematoma expansion in a randomized trial (Anderson *et al.*, 2008); a further large study is underway (INTERACT 2) (Delcourt *et al.*, 2010). Anti-hypertensive treatment is also an important chronic treatment for patients following intracerebral haemorrhage (PROGRESS Collaborative Group, 2001; Arima *et al.*, 2010), but the effects on vascular damage from silent ischaemic lesions is unknown.

Our finding of a significant association between DWI lesions and lobar cerebral microbleeds, and white matter change severity adds to the evidence that, although generally considered to be a haemorrhagic disorder, CAA is also characterized by frequent small infarcts (Menon *et al.*, 2009; Soontornniyomkij *et al*, 2010) (Fig. 3). Since white matter change severity increases with increasing microbleed burden in CAA cohorts and thus with the severity of CAA-related microvasculopathy (Greenberg *et al.*, 2004), infarcts seem to relate to the severity of the underlying small-vessel damage. Furthermore, the relation between DWI lesions and presence of cerebral microbleeds suggests shared pathophysiological pathways for haemorrhagic process and ischaemia (Fig. 3). In CAA, amyloid-β is deposited in small arteries and arterioles, causing thickening of the vessel wall and lumen restriction (Olichney *et al.*, 1995), and endothelial/vascular smooth muscle dysfunction (Dotti *et al.*, 2009). These changes can not only cause vessels to become brittle and prone to microaneurysm formation and blood leakage (Attems *et al.*, 2011), but also to impair local regulation of cerebral blood flow and thus small-vessel or capillary occlusion (Smith *et al.*, 2009). The use of PET with amyloid-binding ligands (such as Pittsburgh B-compound) will help to determine whether a regional correlation exists between amyloid deposition and ischaemia, as in CAA-related haemorrhage (Dierksen *et al.*, 2010). Other mechanisms such as disruption of the blood–brain barrier and active inflammation could also contribute to this active vasculopathic process. Taken together with recent reports of the development of cerebral microbleeds after ischaemic stroke, our data suggest a previously unsuspected and intriguing interplay between the haemorrhagic and ischaemic components in small-vessel diseases (Kidwell *et al.*, 2009) (Fig. 3), suggesting a dynamic continuum between 'microbleeding' and 'microinfarction'.

DWI lesions were found in only 8% of patients with intracerebral haemorrhage who did not fulfil the criteria for probable CAA. This group had a higher prevalence of hypertension and a mixed pattern of cerebral microbleeds (lobar and deep) suggesting

that microinfarction can also result from hypertensive arteriopathy. The association between asymptomatic acute infarcts and hypertensive small-vessel disease was suggested in previous studies, although no definite correlation with hypertension was found (O'Sullivan *et al*, 2003; Kang *et al.*, 2004; Jouvent *et al*, 2011). In our study, it is possible that some of the ischaemic lesions in the non-CAA intracerebral haemorrhage group may have in fact been due to the presence of CAA, as hypertensive arteriopathy and CAA often co-exist. Moreover, although the Boston criteria have been shown to have excellent specificity for CAA, the sensitivity is low, with a negative predictive value of 39%, so that some lobar patients with intracerebral haemorrhage not fulfilling the Boston criteria are likely to have a degree of CAA pathology (Knudsen *et al.*, 2001); this could have weakened the association we found between probable CAA and DWI lesions.

The association between DWI lesions and white matter change burden suggests that at least some white matter change could be due to accumulated microinfarcts (Smith, 2010), or chronic hypoperfusion. Another potential mechanism through which CAA-affected cortical and leptomeningeal vessels can damage white matter is by the entrapment of amyloid-β in perivascular spaces, impairing interstitial drainage pathways from white matter otherwise not directly affected by CAA pathology (Roher *et al.*, 2003).

Our study has several strengths: the systematic evaluation of MRI scans by one trained rater using validated scales, the concomitant use of DWI and apparent diffusion coefficients maps to assess the presence of silent ischaemia and the review of all positive scans by an experienced neuroradiologist. It suffers from limitations due to the lack of pathological confirmation of the ischaemic nature of the DWI lesions and of the CAA pathology as a cause of intracerebral haemorrhage. In all hospital-based intracerebral haemorrhage MRI studies, it is not possible to completely rule out bias as the most severe cases will suffer early mortality or be unable to tolerate an MRI examination. Thus, in the present study, there is likely to be ascertainment bias towards a less severely impaired cohort. However, we found no significant differences in measures of intracerebral haemorrhage severity (including haematoma volume and Glasgow Coma Scores on admission) between included and excluded subjects. Patients excluded had a higher prevalence of symptomatic lobar intracerebral haemorrhage, which could lead to an underestimation of the association between DWI lesions and CAA-related intracerebral haemorrhage.

Finally, we could not rule out the confounding effect of a direct influence of the acute intracerebral haemorrhage in causing

Figure 3 Continued

lesions in the MRI scans of these patients are the latest addition to the spectrum of brain lesions in CAA. In our study, these DWI lesions were located in cortical–subcortical areas of the frontal and temporal lobes; they were small and ovoid or round in shape. (**B**) Inset of a cortical artery and penetrating arterioles and capillaries from the region in the box asterisked (**A**); putative mechanisms of vascular dysfunction and downstream brain lesions in CAA. The deposition of amyloid-β in the vessel wall can disrupt both vessel morphology and function. Our findings of a high prevalence of small DWI-hyperintense lesions indicative of acute ischaemic infarction in patients with CAA can be attributed to multiple potential mechanisms: loss of smooth muscle cells and autoregulation, endothelial dysfunction, wall thickening or direct vessel occlusion. The association of these lesions with cerebral microbleeds suggests shared pathophysiological pathways between the haemorrhagic process and the ischaemia-prone vasculopathy, and an intriguing cross-talk between the haemorrhagic and ischaemic aspects of small-vessel diseases. BBB = blood–brain barrier; WMC = white matter changes.

ischaemia as we did not include a group of patients with CAA without symptomatic lobar haemorrhage, but we excluded any DWI lesions in close proximity to the symptomatic intracerebral haemorrhage, and found no relationship between intracerebral haemorrhage volume and the presence of DWI lesions, making this unlikely.

Our findings raise clinical questions, especially the dilemma about the use or avoidance of anti-thrombotics in patients with intracerebral haemorrhage. Although the risk of anti-coagulation likely overweighs the benefit in most patients with intracerebral haemorrhage due to CAA, the risk versus benefit of anti-platelet agents is less clear (Rosand et al., 2000; Biffi et al., 2010). The presence of DWI lesions may identify a subgroup of patients with intracerebral haemorrhage who might have greater benefit from anti-thrombotic treatment, but clinical studies are needed to address this question.

Our study clearly points to a previously unsuspected high prevalence of acute ischaemia in patients within 3 months of intracerebral haemorrhage, but longitudinal studies with serial clinical examinations and imaging are also needed to further characterize the dynamics, associations and clinical impact. Further studies will determine whether the detection of DWI-positive lesions in CAA can be used as a surrogate marker with value in diagnosis or assessing the severity and progression of the disease.

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