Spectrum of Transient Focal Neurological Episodes in Cerebral Amyloid Angiopathy
Multicentre Magnetic Resonance Imaging Cohort Study and Meta-Analysis

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Background and Purpose—Transient focal neurological episodes (TFNE) are recognized in cerebral amyloid angiopathy (CAA) and may herald a high risk of intracerebral hemorrhage (ICH). We aimed to determine their prevalence, clinical neuroimaging spectrum, and future ICH risk.

Methods—This was a multicenter retrospective cohort study of 172 CAA patients. Clinical, imaging, and follow-up data were collected. We classified TFNE into: predominantly positive symptoms (“aura-like” spreading paraesthesias/positive visual phenomena or limb jerking) and predominantly negative symptoms (“transient ischemic attack-like” sudden-onset limb weakness, dysphasia, or visual loss). We pooled our results with all published cases identified in a systematic review.

Results—In our multicenter cohort, 25 patients (14.5%; 95% confidence interval, 9.6%–20.7%) had TFNE. Positive and negative symptoms were equally common (52% vs 48%, respectively). The commonest neuroimaging features were leukoaraiosis (84%), lobar ICH (76%), multiple lobar cerebral microbleeds (58%), and superficial cortical siderosis/convexity subarachnoid hemorrhage (54%). The CAA patients with TFNE more often had superficial cortical siderosis/convexity subarachnoid hemorrhage (but not other magnetic resonance imaging features) compared with those without TFNE (50% vs 19%; P=0.001). Over a median period of 14 months, 50% of TFNE patients had symptomatic lobar ICH. The meta-analysis showed a risk of symptomatic ICH after TFNE of 24.5% (95% confidence interval, 15.8%–36.9%) at 8 weeks, related neither to clinical features nor to previous symptomatic ICH.

Conclusions—TFNE are common in CAA, include both positive and negative neurological symptoms, and may be caused by superficial cortical siderosis/convexity subarachnoid hemorrhage. TFNE predict a high early risk of symptomatic ICH (which may be amenable to prevention). Blood-sensitive magnetic resonance imaging sequences are important in the investigation of such episodes. (Stroke. 2012;43:00-00.)

Key Words: cerebral amyloid angiopathy ■ cerebral microbleeds ■ intracerebral hemorrhage ■ superficial cortical siderosis

Sporadic cerebral amyloid angiopathy (CAA) is a common age-related cerebral small vessel disease characterized by the progressive deposition of amyloid-β in the wall of cortical and leptomeningeal small arteries.1 CAA is a common cause of spontaneous lobar intracerebral hemorrhage (ICH) and cognitive impairment in the elderly.1

Another characteristic clinical presentation associated with CAA is with transient focal neurological episodes (TFNE), sometimes termed “amyloid spells.”2–4 Most published cases describe recurrent, stereotyped, spreading paraesthesias, usually lasting several minutes.2,3 The recognition of TFNE is of clinical importance because they may have diagnostic value as the most common clinical presentation of CAA other than ICH and may precede symptomatic ICH,5 a risk that could be reduced by avoiding antithrombotic use after misdiagnosis as a transient ischemic attack. The available evidence on TFNE in CAA consists of only case reports and small case series.

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(≤10 patients), 2,3,6–8 which may be subject to publication bias, limiting their generalizability.

Our aims were to determine the prevalence, clinical features, neuroimaging correlates, and future ICH risk associated with CAA-related TFNE in a multicenter CAA cohort. We hypothesized that TFNE are common in CAA and that they signify a high risk of future symptomatic ICH. We pooled our results with all previously published studies identified in a systematic review.

**Subjects and Methods**

**Participants**

We included consecutive patients with CAA diagnosed at 4 stroke centers over defined time periods. The hospitals were University College London Hospitals NHS Foundation Trust (London) (March 2003–September 2011), Addenbrooke’s Hospital (Cambridge) (July 2002–March 2010), Cliniques Universitaires Saint Luc (Brussels) (December 2003–April 2010), and Université Catholique de Louvain (August 2005–March 2009). At participating centers, magnetic resonance imaging (MRI) scanning is routine for all cases of suspected CAA, unless there are contraindications. Our inclusion criteria were: possible, probable, or definite CAA, defined according to the Boston criteria (Supplementary Table I); 9 and a clearly documented history of transient (≤24 hours), fully resolving, focal neurological episodes with no known alternative explanation other than CAA (eg, structural brain lesion, atrial fibrillation, extracranial or intracranial stenosis). We classified TFNE into 2 categories: (1) predominantly positive focal symptoms (“aura-like” spreading paraesthesias, positive visual phenomena, or limb jerking); and (2) predominantly negative focal symptoms (“transient ischemic attack-like” sudden-onset limb weakness, dysphasia, or visual loss). We excluded patients without an adequate medical history or imaging, those not meeting the criteria for CAA, and those with nonfocal transient symptoms (eg, generalized seizures, confusion, disorientation).

**Data Collection**

Cases were ascertained using multiple overlapping methods from prospective clinical databases and radiological reports: 172 patients with possible (n=54), probable (n=115), probable with supportive pathology (n=2), or definite (n=1) CAA were included. Two patients were excluded because of an alternative explanation of TFNE (1 with significant carotid stenosis, 1 with sepsis), 2 because an adequate history was not available, and 11 because episodes were not focal.

Demographic and clinical data were collected using standardized forms. Follow-up information on recurrent cerebrovascular events (including ICH) was obtained from prospective databases and medical records.

**MRI Acquisition and Analysis**

The MRI protocol was standardized in each hospital. Imaging was at 1.5-T field strength for all patients and included T1-weighted, T2-weighted, fluid-attenuated inversion recovery, and T2*-weighted gradient-recalled echo sequences. For some patients, susceptibility-weighted imaging and diffusion-weighted imaging were available. All MRI scans were performed after the TFNE. Images were reviewed blinded to clinical data. Hemorrhagic lesions, ischemic lesions (chronic or acute), and white matter changes (leukoaraiosis) were recorded according to predefined standardized criteria. The presence and distribution of cerebral microbleeds (CMB) were evaluated on T2*-weighted gradient-recalled echo images using the Microbleed Anatomic Rating Scale.10 Previous symptomatic ICH was defined as a symptomatic stroke syndrome associated with imaging evidence of a corresponding ICH (>5 mm in diameter).11 Asymptomatic previous ICH (>5 mm in diameter) was noted. Convexity subarachnoid hemorrhage (cSAH) was defined as linear hypointensity in the subarachnoid space affecting ≥1 cortical sulci of the cerebral convexities on T2* gradient-recalled echo/susceptibility-weighted imaging sequences with corresponding hyperintensity in the subarachnoid space on T1-weighted and/or fluid-attenuated inversion recovery images. Cortical superficial siderosis was defined as linear residues of blood products in the superficial layers of the cerebral cortex showing a characteristic “gyriniform” pattern of low signal on T2* gradient-recalled echo images without corresponding hypointense signal on T1-weighted or fluid-attenuated inversion recovery images. The distribution of superficial siderosis and cSAH was classified as focal (restricted to ≤3 sulci) or disseminated (≥4 sulci).12 Leukoaraiosis was assessed with the 4-step simplified Fazekas rating scale from 0 to 3 (0, no lesions; 1, focal lesions; 2, early confluent; 3, confluent).13 All MRI lesions in the cerebral location corresponding to the clinical features of the TFNE were documented. For patients with a symptomatic ICH after their TFNE, we determined whether the location of the recurrent ICH corresponded to the likely anatomic origin of preceding TFNE.

**Systematic Review: Search Strategy, Selection Criteria, and Data Extraction**

We undertook a systematic review of all published cases of sporadic CAA with clearly documented TFNE and no known alternative explanation other than CAA. Articles published in full in any language were identified through a search of PubMed and Embase (January 1970–October 2011; Supplementary Table II). Reference lists from all included articles also were searched for relevant publications. We extracted and used individual patient data from each study when available (including follow-up data on ICH).

**Statistical Analysis**

Survival analysis was used to examine the time to symptomatic ICH from the start of TFNE using Kaplan-Meier analysis. Cox proportional hazard analyses and log rank tests were used to compare the time to symptomatic ICH according to whether patients had experienced predominantly positive or negative symptoms. The proportional hazards assumption was tested to ensure that there was no evidence of nonproportionality (P>0.2). Multivariable Cox proportional hazards analyses were performed after adjusting for gender and age. Other statistical tests were used as indicated: continuous variables were compared using Student t test (normally distributed) or Mann-Whitney U test (non-normally distributed) and categorical variables using χ2 tests or Fisher exact test.

All statistical tests were 2-sided. Analyses were performed using STATA 11.2 (StataCorp LP). We prepared this report according to STROBE guidelines for observational studies.14

**Results**

**Multicenter Cohort Study**

We identified 172 patients with CAA; of these, 25 (definite CAA=1; probable CAA with supporting pathology=2; probable CAA=18; possible CAA=4; 14.5%; 95% confidence interval [CI], 9.6%–20.7%) had a history of TFNE, meeting the study inclusion criteria (Table 1).

**Clinical Features of the Episodes**

Thirteen patients (52%) had predominantly positive (“aura-like”) symptoms; 12 (48%) had predominantly negative (“transient ischemic attack-like”) symptoms (Supplementary Table III). The most common positive symptom was transient paraesthesias (with or without numbness) in 8 patients (32%); a gradual spread to continuous body parts was described in 5 of these. Sensory symptoms affected the mouth or hand in all cases, and both regions in 4 cases. Four patients (16%) had limb-jerking episodes and 4 (16%) patients had visual disturbances involving monocular blurred vision, flickering, or flashing lights, transient “zig-zags” (teichopsia), or visual
loss. Four (16%) patients had focal weakness and 7 (28%) had dysphasia. Most participants (17/25; 68%) had multiple (≥2) stereotyped episodes. The episodes typically lasted <10 minutes and in 70% of the patients they lasted <30 minutes. In 7 patients (28%), antplatelets or anticoagulants were started after TFNE.

Neuroimaging Findings and Correlation With Symptoms
All except 1 patient (with pathologically proven CAA) had a brain MRI undertaken after the TFNE (Supplementary Table I); the median time from the episodes to MRI was 7 days (interquartile range, 6.5–30 days). Nineteen patients (76%) had evidence of lobar ICH: 9 patients (36%) had evidence of acute lobar ICH, whereas 10 patients (40%) had evidence of chronic lobar ICH. Only 1 patient had a previous cortical infarct. Multiple strictly lobar CMB were present in 14 patients (58%), cortical superficial siderosis, or cSAH in 14 cases (58%). Diffusion-weighted imaging was available in 17 patients (71%) and susceptibility-weighted imaging was available in 10 patients (42%). Among patients with diffusion-weighted imaging, 7 (41%) were scanned within 2 weeks of the start of TFNE; acute ischemia was noted in only 1 of these patients. In 23 patients (92%; patients 1–4, 6–16, and 18–25) the clinical features of the TFNE could be anatomically correlated with hemorrhagic cortical or cortico-subcortical radiological lesions (Figures 1, 2).

Table 1. Demographic, Clinical, and Magnetic Resonance Imaging Characteristics of Multicentre Cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values (n=25)</th>
</tr>
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<tbody>
<tr>
<td><strong>Clinical demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age, mean (95% CI), y</td>
<td>69.7 (66.9 to 72.5)</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>14 (56)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Smoking history (%)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Using antithrombotics at onset of TFNE (%)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>Previous symptomatic ICH (%)</td>
<td>8 (32)</td>
</tr>
<tr>
<td><strong>Clinical features of TFNE</strong></td>
<td></td>
</tr>
<tr>
<td>Predominantly positive symptoms (%)</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Predominantly negative symptoms, ”TIA-like“ (%)</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Associated headache (%)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Patients with &gt;1 type of attack (%)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Patients with multiple (≥2) episodes (%)</td>
<td>17 (68)</td>
</tr>
<tr>
<td><strong>Episode duration</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;6 min (%)</td>
<td>11 (44)</td>
</tr>
<tr>
<td>6–19 min (%)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>≥20 min (%)</td>
<td>9 (36)</td>
</tr>
<tr>
<td><strong>MRI findings (n=24)</strong></td>
<td></td>
</tr>
<tr>
<td>Median time (d) from episodes to MRI (interquartile range)</td>
<td>7 (6.5–30)</td>
</tr>
<tr>
<td>Superficial cortical siderosis (%)</td>
<td>12 (50)</td>
</tr>
<tr>
<td>Focal, ≤3 sulci (%)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Disseminated, &gt;4 sulci (%)</td>
<td>8 (33)</td>
</tr>
<tr>
<td>cSAH (%)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>cSAH or superficial cortical siderosis (%)</td>
<td>14 (58)</td>
</tr>
<tr>
<td>Acute ischemic lesions</td>
<td>1</td>
</tr>
<tr>
<td>Evidence of lobar ICH (%)</td>
<td>19 (76)</td>
</tr>
<tr>
<td>Acute lobar ICH evidence (%)</td>
<td>9 (36)</td>
</tr>
<tr>
<td>Chronic lobar ICH evidence (%)</td>
<td>10 (40)</td>
</tr>
<tr>
<td>Multiple lobar cerebral microbleeds, ≥2 (%)</td>
<td>14 (58)</td>
</tr>
<tr>
<td>Leukoaraiosis: Fazekas category (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4 (16)</td>
</tr>
<tr>
<td>1</td>
<td>9 (36)</td>
</tr>
<tr>
<td>2</td>
<td>8 (32)</td>
</tr>
<tr>
<td>3</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Antiplatelets/anticoagulants given after TFNE (%)</td>
<td>7 (28)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Aspirin plus clopidogrel</td>
<td>1 (4)</td>
</tr>
<tr>
<td><strong>Follow-up information (n=24)</strong></td>
<td></td>
</tr>
<tr>
<td>Median follow-up duration (interquartile range)</td>
<td>14 mo (4–35 mo)</td>
</tr>
<tr>
<td>Occurrence of symptomatic ICH (%)</td>
<td>12 (50)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; cSAH, convexity subarachnoid hemorrhage; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; TFNE, transient focal neurological episodes; TIA, transient ischemic attack.
Neuropathological Findings

Pathological samples were available in 3 of the 25 patients (patients 5, 17, and 18); hematoxylin and eosin staining and immunohistochemical detection of amyloid-β revealed moderate to severe CAA without vasculitis. In patient 5, who presented with multiple recurrent episodes of sudden numbness of the right hand, a biopsy of the left temporal lobe revealed multiple cortical microinfarcts, Alzheimer-type pathology, and severe CAA (without vasculitis).

Risk of Future ICH

Follow-up data were available in all except 1 patient with TFNE over a median duration of 14 months (interquartile range, 4–35 months), during which 12 of 24 patients (50%) had symptomatic spontaneous lobar ICH; 3 had multiple consecutive ICH. Only 1 patient had an ischemic stroke. For 7 patients with ICH after TFNE (58%), the subsequent ICH was in a cortical area corresponding to the likely origin of their TFNE (based on the clinical presentation). Kaplan-Meier ICH analysis indicated that within 2 months of the TFNE, 37.5% (95% CI, 21.6%–59.7%) of the patients experienced a symptomatic ICH (Figure 3A). Patients with a subsequent ICH did not differ from those without future ICH, either in clinical and imaging characteristics or in antiplatelet or anticoagulant use (data not shown).

Characteristics of CAA Patients With TFNE vs Those Without TFNE

Patients with and without TFNE were not significantly different in age, prevalence of vascular risk factors, antithrombotic use, or previous history of symptomatic lobar ICH (Table 2). Among neuroimaging characteristics, only the prevalence of superficial cortical siderosis was significantly higher in patients with TFNE compared with those without (50% vs 19%; \( P=0.001 \)). Disseminated cortical superficial siderosis (≥4 sulci) was more than twice as common in CAA patients with TFNE compared with those without (33% vs 14%; \( P=0.005 \)). There were no significant differences in
Table 2. Characteristics of Patients With Cerebral Amyloid Angiopathy and Transient Focal Neurological Episodes vs Cerebral Amyloid Angiopathy Patients Without Transient Focal Neurological Episodes

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CAA Patients With TFNE (n=25)</th>
<th>CAA Patients Without TFNE (n=147)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (95% CI), y</td>
<td>69.7 (66.9–72.5)</td>
<td>73.1 (71.4–74.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>14 (56)</td>
<td>73 (50)</td>
<td>0.558</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>13 (52)</td>
<td>92 (67)</td>
<td>0.145</td>
</tr>
<tr>
<td>Using antithrombotics (%)</td>
<td>8 (32)</td>
<td>41 (30)</td>
<td>0.801</td>
</tr>
<tr>
<td>Previous symptomatic ICH (%)</td>
<td>8 (32)</td>
<td>54 (39)</td>
<td>0.532</td>
</tr>
<tr>
<td>Neuroimaging findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial cortical siderosis (%)</td>
<td>12 (50)</td>
<td>24 (19)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Focal (&lt;3 sulci) (%)</td>
<td>4 (17)</td>
<td>10 (8)</td>
<td>0.187</td>
</tr>
<tr>
<td>Disseminated (≥4 sulci) (%)</td>
<td>8 (33)</td>
<td>14 (11)</td>
<td>0.005*</td>
</tr>
<tr>
<td>cSAH (%)</td>
<td>4 (17)</td>
<td>8 (7)</td>
<td>0.106</td>
</tr>
<tr>
<td>Acute ischaemic lesions (%)</td>
<td>1 (6)</td>
<td>12 (11)</td>
<td>0.512</td>
</tr>
<tr>
<td>Chronic lobar ICH evidence (%)</td>
<td>10 (40)</td>
<td>72 (53)</td>
<td>0.248</td>
</tr>
<tr>
<td>Acute lobar ICH evidence (%)</td>
<td>9 (36)</td>
<td>65 (48)</td>
<td>0.250</td>
</tr>
<tr>
<td>Multiple lobar CMB (≥2) (%)</td>
<td>14 (58)</td>
<td>71 (56)</td>
<td>0.975</td>
</tr>
<tr>
<td>N of CMB, median (IQR range)</td>
<td>3 (0–16)</td>
<td>2.5 (0–8)</td>
<td>0.552</td>
</tr>
<tr>
<td>Leukoaraiosis: Fazekas category (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4 (16)</td>
<td>25 (19)</td>
<td>0.981</td>
</tr>
<tr>
<td>1</td>
<td>9 (36)</td>
<td>43 (32)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8 (32)</td>
<td>43 (32)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4 (16)</td>
<td>22 (17)</td>
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</tr>
</tbody>
</table>

CAA indicates cerebral amyloid angiopathy; CI, confidence interval; CMB, cerebral microbleed; cSAH, convexity subarachnoid hemorrhage; IQR, interquartile range; TFNE, transient focal neurological episodes.

other neuroimaging findings (acute ischemic lesions, leukoaraiosis, cSAH, presence of multiple lobar CMB, presence of ICH, or CMB count) between patients with and without TFNE.

Systematic Review and Meta-Analysis

We included 21 studies in the systematic review containing data on 68 patients with CAA-related TFNE (Supplementary Figure 1). Fifteen studies (6 case series and 9 case reports; n=43) had adequate follow-up data. This population was similar in age, gender, and proportion of cases with a history of symptomatic ICH to our multicenter cohort.

A meta-analysis of these 15 studies showed a future risk of symptomatic ICH of 17.2% (95% CI, 8.5%–32.7%) at 2 months (Figure 3B). Once these data are pooled with our cohort, the 2-month risk of symptomatic ICH increases to 24.5% (95% CI, 15.8%–36.9%; Figure 3C). Patients with negative symptoms had a similar risk of future ICH as patients with positive symptoms (hazard ratio, 0.91; 95% CI, 0.40–2.08; P=0.83). There was a borderline significant lower risk of future ICH among patients with previous symptomatic ICH compared with those without (hazard ratio, 0.47; 95% CI, 0.22–1.01).

Previously published studies had a significantly higher proportion of “aura-like” positive spreading sensory disturbances compared with our multicenter cohort (82% vs 36%; P<0.0001; Figure 4).

Discussion

In our multicenter cohort study we found TFNE in 14% of patients with CAA. Our study confirms previous reports that CAA-related TFNE are mostly recurrent, stereotyped, and brief (usually <30 minutes).2,3 However, unlike published studies, in which “aura-like” sensory episodes seem to be most frequent, in our cohort negative symptoms were just as common. This difference might reflect previous publication bias in favor of CAA cases with spreading sensory phenomena not typical of transient ischemic attacks. All episodes of aura-like sensory symptoms in our cohort (n=8) involved the face or hand; 3 involved the corner of the mouth and the hand consistent with a cortical cheiro-oral syndrome. In 2 of these, cortical siderosis/cSAH were present over the frontal or parietal lobes, whereas the third case had multiple lobar CMB. Although the numbers of cases was small, the cheiro-oral pattern may be rather characteristic of sensory CAA-related TFNE.

The clinical features of the episodes indicate a cortical rather than a subcortical origin; moreover, they were often correlated anatomically with hemorrhagic MRI lesions, including CMB, superficial cortical siderosis, and lobar ICH. Thus, TFNE are probably related to the hemorrhagic rather than the ischemic components of CAA; possible mechanisms include focal seizure-like activity or migraine aura-like cortical spreading depression, as suggested by previously published small case series.2,3,15 Twenty-three patients in our cohort had
hemorrhagic imaging findings in a neuroanatomical location, corresponding to their TFNE symptoms; 8 had superficial cortical siderosis, reflecting previous episodes of acute bleeding in the subarachnoid space of adjacent cortical sulci. Three other recent case series also have emphasized the possible role of nontraumatic sSAH in CAA-related TFNE. Our finding that superficial cortical siderosis was significantly more common in CAA patients with TFNE than in those without (P = 0.001) provides strong evidence that this pattern of bleeding is likely to be an important cause of TFNE.

Nevertheless, a role for ischemic lesions in CAA-related TFNE cannot be ruled out by our study: small (apparently asymptomatic) ischemic lesions have been detected in vivo in clinically probable CAA, and “microinfarcts” are a frequent neuropathological finding in the brains of patients with CAA. Because not all cases in our study had diffusion-weighted imaging soon after the onset of TFNE, we may have underestimated the contribution from small acute ischemic lesions.

We report a strikingly high early risk of symptomatic lobar ICH (37.5% at 2 months) after CAA-related TFNE, which we confirmed in a meta-analysis of our data with all published studies. We found only a borderline difference in the risk of ICH among patients with previous symptomatic ICH compared with those without, suggesting that TFNE, rather than simply the presence of CAA with previous symptomatic ICH (with a known recurrent ICH risk of ~10% per year) are an independent marker of high early future ICH risk. TFNE in CAA thus may be a clinical marker for cerebral areas of focally active and severe CAA pathology, with more vascular leakage leading to an increased risk of future ICH. This is supported by our finding of a significantly higher prevalence of superficial cortical siderosis in CAA patients with TFNE, because superficial siderosis is hypothesized to result from recurrent bleeding into the subarachnoid space, leading to subpial accumulation of blood-breakdown products. However, the role of superficial siderosis as a prognostic imaging marker of increased ICH risk in CAA requires further study.

Although in 58% of patients with ICH after TFNE the new hematoma was located in a cortical area corresponding to the likely origin of their TFNE (based on the clinical presentation), further work is needed to establish whether this apparent clustering of ICH in brain regions implicated by TFNE symptoms is greater than predicted by chance.

Our study has several potential limitations. We may have underestimated the true prevalence of CAA-related TFNE because of the retrospective study design; further large prospective studies with systematic enquiry about previous TFNE are needed. Some of our CAA cohort may have been misdiagnosed because of the imperfect specificity of the Boston criteria (particularly the “possible CAA” category). MRI was performed at different times from TFNE onset; this, combined with the lack of availability of acute diffusion-weighted imaging sequences in all cases, may have influenced the detection of hemorrhagic over ischemic lesions. We also acknowledge the potential for referral, selection, and publication bias in the cases identified in the systematic review. Our multicenter cohort results might not be generalizable to all CAA patients, but only to those presenting to vascular neurology services and those in whom other possible causes of transient focal neurological symptoms have been excluded. Although this study includes the largest number of CAA-related TFNE cases to date, we did not have sufficient statistical power to definitively determine potential predictors for ICH. Finally, an important question is whether CAA patients with TFNE have an increased risk of future symptomatic ICH compared with those without TFNE, but the retrospective design and focus on outcome after TFNE in our study meant that we were unable to undertake this comparison.

Conclusions

We have shown that TFNE are common in CAA and signify a very high early future risk of ICH. Hence, their diagnosis has important clinical implications. Our findings clearly suggest a key role for T2* gradient-recalled echo MRI (or other blood-sensitive sequences) in the investigation of patients with unexplained TFNE, especially in individuals without known risk factors for transient ischemic attack. The very high early risk of lobar ICH after TFNE in CAA may be an opportunity to commence preventive strategies. We suggest clinicians should discontinue and avoid administering antiplatelets or anticoagulants in cases of TFNE with imaging evidence of CAA, even if the episodes seem clinically likely to be ischemic. Because TFNE were observed in patients without a history of symptomatic ICH, they also may prove to be a useful diagnostic marker of CAA, potentially allowing diagnosis earlier in its disease course.

Sources of Funding

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Disclosures

None.

References


Spectrum of Transient Focal Neurological Episodes in Cerebral Amyloid Angiopathy: Multicentre Magnetic Resonance Imaging Cohort Study and Meta-Analysis
Andreas Charidimou, Andre Peeters, Zoe Fox, Simone M. Gregoire, Yves Vandermeeren, Patrice Laloux, Hans R. Jäger, Jean-Claude Baron and David J. Werring

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Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2012/07/12/STROKEAHA.112.657759.DC1
http://stroke.ahajournals.org/content/suppl/2013/10/02/STROKEAHA.112.657759.DC2

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SUPPLEMENTARY MATERIAL
Supplementary Table 1. Classic and modified Boston criteria for diagnosis of cerebral amyloid angiopathy (CAA) (Linn et al., 2010).

1. Definite CAA
Full post-mortem examination demonstrating:
- Lobar, cortical, or cortical-subcortical haemorrhage
- Severe CAA with vasculopathy
- Absence of other diagnostic lesion

2. Probable CAA with supporting pathology
Clinical data and pathologic tissue (evacuated haematoma or cortical biopsy) demonstrating:
- Lobar, cortical, or cortical-subcortical haemorrhage
- Some degree of CAA in specimen
- Absence of other diagnostic lesion

3. Probable CAA
Clinical data and MRI or CT demonstrating:
- Multiple haemorrhages restricted to lobar, cortical, or cortical-subcortical regions (cerebellar haemorrhage allowed) OR
- Single lobar, cortical, or cortical-subcortical haemorrhage and focal or disseminated superficial siderosis
- Age ≥55 years
- Absence of other cause of haemorrhage

4. Possible CAA
Clinical data and MRI or CT demonstrating:
- Single lobar, cortical, or cortical-subcortical haemorrhage OR
- Focal or disseminated superficial siderosis
- Age ≥55 years
- Absence of other cause of haemorrhage

Other causes of haemorrhage include: antecedent head trauma, haemorrhagic transformation of an ischemic stroke, arteriovenous malformation, haemorrhagic tumour, warfarin therapy with international normalisation ratio > 3 and vasculitis

Focal siderosis: siderosis restricted to 3 or fewer sulci.
Disseminated siderosis: siderosis affecting at least 4 sulci
Supplementary Table 2. Electronic database search strategies

<table>
<thead>
<tr>
<th>No</th>
<th>Search history</th>
<th>Results</th>
</tr>
</thead>
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<tr>
<td></td>
<td><strong>PubMed search strategy</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>(amyloid angiopathy OR cerebral amyloid angiopathy) AND (seizure OR seizures OR episode OR episodes OR transient OR attack OR attacks OR aura OR TIA OR subarachnoid OR sub-arachnoid OR SAH OR cSAH OR fSAH OR siderosis OR hemosiderosis OR haemosiderosis OR spells)</td>
<td>202</td>
</tr>
<tr>
<td>2</td>
<td>Limit to: Publication Date from 1970/01/01</td>
<td>202</td>
</tr>
<tr>
<td></td>
<td><strong>Embase search strategy</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>(amyloid angiopathy or cerebral amyloid angiopathy).tw.</td>
<td>1911</td>
</tr>
<tr>
<td>2</td>
<td>Limit 1 to (human and yr=&quot;1970 -Current&quot;)</td>
<td>1472</td>
</tr>
<tr>
<td>3</td>
<td>(seizure or seizures or episode or episodes or transient or attack or attacks or aura or TIA or subarachnoid or sub-arachnoid or SAH or cSAH or fSAH or siderosis or h?emosiderosis or spells).tw.</td>
<td>522882</td>
</tr>
<tr>
<td>4</td>
<td>Limit 3 to (human and yr=&quot;1970 -Current&quot;)</td>
<td>270996</td>
</tr>
<tr>
<td>5</td>
<td>2 and 4</td>
<td>175</td>
</tr>
</tbody>
</table>

Search software used: OvidSP_UI03.04.02.112, SourceID 54875
Supplementary Figure 1. Flow chart of study selection for the systematic review. Twenty-one studies were included in our systematic review.²⁻²² Three studies had no extractable individual patient data.²,¹⁶,¹⁷ Fifteen studies (six case series and nine case reports; n=43) had follow-up data.²,⁴⁻⁶,¹⁰⁻¹⁵,¹⁸⁻²²
Supplementary Table 3. Individual clinical patient data of multicentre cohort.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Description</th>
<th>Duration</th>
<th>Classification *</th>
<th>Number</th>
<th>Clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>68/f</td>
<td>Left arm weakness; paraesthesias around the left side of the mouth and slurred speech</td>
<td>1-2 min</td>
<td>Positive</td>
<td>15</td>
<td>Right frontal ICH after several days; left frontal ICH at 12 months; left parietal ICH at 3 years</td>
</tr>
<tr>
<td>P2</td>
<td>76/m</td>
<td>Tingling of the thumb, index and middle finger of the right hand; As above with expressive dysphasia and right facial droop</td>
<td>1-2 min</td>
<td>Positive</td>
<td>Multiple 1</td>
<td>No cerebrovascular event</td>
</tr>
<tr>
<td>P3</td>
<td>68/f</td>
<td>Spreading numbness and pins-and-needles over the left hand with slight weakness; right-sided headache; tingling over the left corner of the mouth Acute onset episodes of left hemiparesis (arm and face)</td>
<td>Several minutes 6 hours</td>
<td>Positive</td>
<td>Multiple over 3-4 weeks 2</td>
<td>Left frontal ICH at 10 weeks</td>
</tr>
<tr>
<td>P4</td>
<td>61/f</td>
<td>Numbness and a tingling sensation around the right corner of the mouth; after 2-3 minutes this spread to the right hand. Numbness over the right side of the lips vanishes while the right hand numbness continues for another 5-10 minutes</td>
<td>10-15 min</td>
<td>Positive</td>
<td>&gt;3-4</td>
<td>Right frontal ICH several days after the first episodes</td>
</tr>
<tr>
<td>P5</td>
<td>59/m</td>
<td>Sudden numbness of the right hand; left temporal headache and blurred vision in the left eye, with flickering lights</td>
<td>4-5 min</td>
<td>Positive</td>
<td>Multiple (4/day)</td>
<td>Patient developed cognitive impairment</td>
</tr>
<tr>
<td>P6</td>
<td>72/f</td>
<td>“Pressure feeling” in the left side of the roof of the mouth migrating towards the left ear; disorientated and unsteady</td>
<td>2-30 min</td>
<td>Positive</td>
<td>5-7 over 6 months</td>
<td>No cerebrovascular event</td>
</tr>
<tr>
<td>P7</td>
<td>74/m</td>
<td>Tingling in the ulnar fingers of the left hand, migrating up the arm and into the neck; then into the left side of the tongue and mouth (with difficulty moving the tongue)</td>
<td>2-3 min</td>
<td>Positive</td>
<td>3</td>
<td>Right frontal-parietal ICH at 1 month</td>
</tr>
<tr>
<td>P8</td>
<td>73/m</td>
<td>Left-sided arm jerking (sometimes associated with tingling) followed by confusion and weakness of this arm</td>
<td>2-3 hours</td>
<td>Positive</td>
<td>Multiple</td>
<td>No cerebrovascular event</td>
</tr>
<tr>
<td>P9</td>
<td>52/m</td>
<td>“Uncontrolled shaking” of the right arm</td>
<td>2 min</td>
<td>Positive</td>
<td>1</td>
<td>Left parietal ICH at 6 weeks</td>
</tr>
<tr>
<td>P10</td>
<td>66/m</td>
<td>Right hand jerking</td>
<td>1 min</td>
<td>Positive</td>
<td>1</td>
<td>Left posterior temporal ICH at 6 days</td>
</tr>
<tr>
<td>P11</td>
<td>73/f</td>
<td>Episodes of “zigzags” in the right visual field Frequent bilateral headaches over the top of the head</td>
<td>1-2 seconds</td>
<td>Positive</td>
<td>Multiple (few/day)</td>
<td>No cerebrovascular event</td>
</tr>
<tr>
<td>P12</td>
<td>67/f</td>
<td>Visual disturbance (on examination had a lower right homonymous quadrantopia) Numbness in the R hand radiating to R upper limb and then to R lower limb Numbness of the right upper limb and face, confusion</td>
<td>30 min</td>
<td>Positive (atypical spreading onset)</td>
<td>2</td>
<td>Left frontal and right temporoparietal ICH while episodes were on-going</td>
</tr>
<tr>
<td>P13</td>
<td>66/m</td>
<td>Non-fluent dysphasia</td>
<td>10-15 min</td>
<td>Negative</td>
<td>7-8</td>
<td>No cerebrovascular event</td>
</tr>
<tr>
<td>P14</td>
<td>66/m</td>
<td>Sudden onset of left arm weakness Sudden onset of left arm weakness accompanied by left facial droop and slurring of speech</td>
<td>5 min 20 min</td>
<td>Negative</td>
<td>2</td>
<td>No cerebrovascular event</td>
</tr>
<tr>
<td>Case</td>
<td>Age/gender</td>
<td>Diagnosis</td>
<td>Onset, duration</td>
<td>Outcome</td>
<td>Comment</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>------------</td>
<td>-----------</td>
<td>----------------</td>
<td>---------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>P15</td>
<td>71/m</td>
<td>Non-fluent dysphasia (sudden onset of speech arrest followed by slurred speech and some inappropriate words)</td>
<td>5 min several hours</td>
<td>Negative</td>
<td>1</td>
<td>No cerebrovascular event</td>
</tr>
<tr>
<td>P16</td>
<td>68/m</td>
<td>Weakness and clumsiness of the right hand; drooping of the right side of the mouth; and slurred speech. In the second episode the hand was not affected</td>
<td>2-3 days</td>
<td>Negative</td>
<td>2</td>
<td>No cerebrovascular event</td>
</tr>
<tr>
<td>P17</td>
<td>76/f</td>
<td>Non-fluent dysphasia (unable to speak)</td>
<td>90 min</td>
<td>Negative</td>
<td>3</td>
<td>Right frontal ICH at 2 weeks</td>
</tr>
<tr>
<td>P18</td>
<td>78/m</td>
<td>Right limb weakness</td>
<td>Several minutes</td>
<td>Negative</td>
<td>8-10</td>
<td>Left frontal ICH at 10 weeks</td>
</tr>
<tr>
<td>P19</td>
<td>69/m</td>
<td>Left-sided weakness (face, arm, leg) and dysarthria</td>
<td>Several minutes</td>
<td>Negative</td>
<td>1</td>
<td>Admitted with sudden-onset left hand weakness (ischaemic stroke)</td>
</tr>
<tr>
<td>P20</td>
<td>77/f</td>
<td>Dysphasia and light headedness</td>
<td>30 min</td>
<td>Negative</td>
<td>2</td>
<td>One further episode at 1 week-aspirin stopped</td>
</tr>
<tr>
<td>P21</td>
<td>75/f</td>
<td>Non-fluent dysphasia</td>
<td>5-6 min</td>
<td>Negative</td>
<td>Multiple</td>
<td>No cerebrovascular event</td>
</tr>
<tr>
<td>P22</td>
<td>76/f</td>
<td>Non-fluent dysphasia</td>
<td>1-2 days</td>
<td>Negative</td>
<td>1</td>
<td>Left frontal-parietal ICH at 5 months</td>
</tr>
<tr>
<td>P23</td>
<td>75/f</td>
<td>Non-fluent dysphasia followed by transient amnesia</td>
<td>5-6 min</td>
<td>Negative</td>
<td>1</td>
<td>No cerebrovascular event</td>
</tr>
<tr>
<td>P24</td>
<td>78/m</td>
<td>Complained of blurred vision; on examination had a left homonymous hemianopia</td>
<td>2-3 hours</td>
<td>Negative</td>
<td>1</td>
<td>Symptomatic right occipital ICHs at 2 days and at 30 months</td>
</tr>
<tr>
<td>P25</td>
<td>59/m</td>
<td>Focal partial motor seizure with jerking of the left upper limb</td>
<td>Several minutes</td>
<td>Positive</td>
<td>2</td>
<td>Right frontal ICH on the same day</td>
</tr>
</tbody>
</table>

ICH = Intracerebral haemorrhage
*As defined in the “Materials and Methods” section
†All ICHs were lobar (i.e. cortical-subcortical).
**Supplementary Table 4.** Individual neuroimaging data of multicentre cohort.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Acute infarct/DWI (+) lesion</th>
<th>Chronic cortical infarct</th>
<th>Evidence of lobar ICH&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Superficial siderosis (extension †/location)</th>
<th>cSAH</th>
<th>Lobar CMBs ‡</th>
<th>WMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>None/None</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Focal/R</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>P2</td>
<td>None/None</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>&gt;10</td>
<td>Yes</td>
</tr>
<tr>
<td>P3</td>
<td>None/NA</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>P4</td>
<td>None/NA</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>&gt;10 (including L frontal-parietal)</td>
<td>Yes</td>
</tr>
<tr>
<td>P5&lt;sup&gt;*&lt;/sup&gt;</td>
<td>None/NA</td>
<td>None</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>P6</td>
<td>None/None</td>
<td>R parietal-occipital</td>
<td>No</td>
<td>Focal/ R (including parietal)</td>
<td>No</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>P7</td>
<td>None/None</td>
<td>R frontal + R frontal-parietal</td>
<td>No</td>
<td>Disseminated/ R&gt;L (including R frontal + parietal convexity)</td>
<td>No</td>
<td>Posterior medial focal</td>
<td>&gt;10</td>
</tr>
<tr>
<td>P8</td>
<td>None/None</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>&gt;10 (including L frontal-parietal)</td>
<td>Yes</td>
</tr>
<tr>
<td>P9</td>
<td>None/NA</td>
<td>None</td>
<td>No</td>
<td>L parietal</td>
<td>No</td>
<td>10 (including L frontal)</td>
<td>Yes</td>
</tr>
<tr>
<td>P10</td>
<td>None/None</td>
<td>R occipital</td>
<td>No</td>
<td>L temporal (extending to L frontal-parietal)</td>
<td>No</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td>P11</td>
<td>None/NA</td>
<td>L parietal-occipital</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>P12</td>
<td>None/None</td>
<td>L frontal</td>
<td>No</td>
<td>Disseminated/ R (including parietal)</td>
<td>No</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>P13</td>
<td>None/NA</td>
<td>L parietal</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>P14</td>
<td>None/None</td>
<td>L temporal</td>
<td>No</td>
<td>Disseminated/ R+L</td>
<td>No</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td>P15</td>
<td>None/NA</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>&gt;20 (including L temporal)</td>
<td>Yes</td>
</tr>
<tr>
<td>P16</td>
<td>None/NA</td>
<td>R frontal</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>&gt;5 (including L frontal-parietal)</td>
<td>Yes</td>
</tr>
<tr>
<td>P17&lt;sup&gt;*&lt;/sup&gt;</td>
<td>None/None</td>
<td>None</td>
<td>No</td>
<td>R frontal</td>
<td>No</td>
<td>7-10</td>
<td>Yes</td>
</tr>
<tr>
<td>P18&lt;sup&gt;*&lt;/sup&gt;</td>
<td>None/NA</td>
<td>N/A</td>
<td>L frontal</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>P19</td>
<td>None/None</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>&gt;50</td>
<td>Yes</td>
</tr>
<tr>
<td>P20</td>
<td>None/R cerebellar + L parietal</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Disseminated/ L&gt;R</td>
<td>Yes</td>
</tr>
<tr>
<td>P21</td>
<td>None/None</td>
<td>R frontal + L paracentral lobule</td>
<td>No</td>
<td>Disseminated/ R+L</td>
<td>No</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>P22</td>
<td>None/None</td>
<td>R frontal-parietal + R parietal + R occipital</td>
<td>No</td>
<td>Disseminated/ L</td>
<td>No</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>P23</td>
<td>None/None</td>
<td>R frontal</td>
<td>No</td>
<td>Disseminated/ L&gt;R</td>
<td>No</td>
<td>&gt;50</td>
<td>Yes</td>
</tr>
<tr>
<td>P24</td>
<td>None/None</td>
<td>R occipital</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>15</td>
<td>Yes</td>
</tr>
<tr>
<td>P25</td>
<td>None/None</td>
<td>R frontal</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>1</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Patients with pathologically proven cerebral amyloid angiopathy

† All ICHs detected were lobar (i.e. cortical-subcortical). Focal superficial siderosis = siderosis restricted to 3 or fewer sulci; Disseminated superficial siderosis = siderosis affecting at least 4 sulci.

‡ None of the patients had deep CMBs
**Supplementary Table 5** Transient focal neurological episodes (TFNE) in sporadic cerebral amyloid angiopathy (CAA): summary of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of participants/study</th>
<th>Total study population/number with CAA and TFNE/number with follow-up data*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emsley et al., 2012</td>
<td>Case report</td>
<td>1/1/1</td>
</tr>
<tr>
<td>Raposo et al., 2010</td>
<td>Consecutive patients with cSAH and no apparent cause</td>
<td>10/10/10</td>
</tr>
<tr>
<td>Profice et al., 2011</td>
<td>Case report</td>
<td>1/1/1</td>
</tr>
<tr>
<td>Gasca-Salas, 2011</td>
<td>Case report</td>
<td>1/1/1</td>
</tr>
<tr>
<td>Dhollander et al., 2011</td>
<td>Two cases with <em>in vivo</em> amyloid imaging (PET)</td>
<td>2/2/2</td>
</tr>
<tr>
<td>Finelli, 2010</td>
<td>Case series of patients with cSAH</td>
<td>4/4/1</td>
</tr>
<tr>
<td>Brunot et al., 2010</td>
<td>Case series with a transient neurological deficit due to cSAH, identified from the Dijon Stroke Registry over 4 years</td>
<td>7/7/7</td>
</tr>
<tr>
<td>Izenberg et al., 2009</td>
<td>Case series of TIA-mimics, referred for &quot;crescendo transient ischemic attacks&quot;.</td>
<td>4/4/4</td>
</tr>
<tr>
<td>Kleinig et al., 2008</td>
<td>Case series of aura-like symptoms in the elderly</td>
<td>4/3/3</td>
</tr>
<tr>
<td>Katoh et al., 2007</td>
<td>Two cases presented with seizure-like episodes, found to have cSAH and then an ICH occurred</td>
<td>2/2/2</td>
</tr>
<tr>
<td>Karabatsou et al., 2007</td>
<td>Case series of CAA with cSAH and superficial siderosis</td>
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<tr>
<td>Roch et al., 2005</td>
<td>Case series of TFNE related to CAA</td>
<td>6/5/0</td>
</tr>
<tr>
<td>Peysson et al., 2003</td>
<td>Case report</td>
<td>1/1/0</td>
</tr>
<tr>
<td>Greenberg et al., 1996</td>
<td>Prospectively obtained T2*-GRE MRI on 15 elderly patients with lobar ICH on CT</td>
<td>15/1/0</td>
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<tr>
<td>Scully et al., 1996</td>
<td>Case report</td>
<td>1/1/1</td>
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<tr>
<td>Greenberg et al., 1993</td>
<td>Case series exploring presentations of CAA without lobar ICH</td>
<td>7/5/4</td>
</tr>
<tr>
<td>Chamouard et al., 1988</td>
<td>Two cases of CAA with TIA-s who died of ICH</td>
<td>2/2/2</td>
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<tr>
<td>Smith et al., 1985</td>
<td>Case report</td>
<td>1/1/1</td>
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<tr>
<td>Beitzke et al., 2011</td>
<td>Patients with non-traumatic cSAH (single tertiary centre radiological database)</td>
<td>24/5/0</td>
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<tr>
<td>Kumar et al., 2010</td>
<td>Cohort with localized non-traumatic cSAH</td>
<td>29/9+NA</td>
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<tr>
<td>Okazaki et al., 1979</td>
<td>Clinicopathological study of sporadic CAA</td>
<td>23/3/0</td>
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</table>

Abbreviations: cSAH = cortical subarachnoid haemorrhage; ICH=intracerebral haemorrhage; T2*-GRE=T2*-weighted gradient recalled echo; TIA= transient ischaemic attack. NA= not available.

*Estimated from published information where necessary, as marked.
References


脳アミロイド血管症における一過性局在性神経学的エピソード多施設共同磁気共鳴画像法コホート研究およびメタ解析

Spectrum of Transient Focal Neurological Episodes in Cerebral Amyloid Angiopathy
Multicentre Magnetic Resonance Imaging Cohort Study and Meta-Analysis

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Abstract

脳アミロイド血管症における一過性局在性神経学的エピソード（TFNE）は脳アミロイド血管症（CAA）において認められ、脳内出血（ICH）の高リスクの予兆である可能性がある。我々は、その有病率、臨床的神経画像スペクトル、および将来のICHリスクを明確にすることを目的とした。

方法：これは172例のCAA患者を対象とした多施設共同後ろ向きコホート研究である。臨床データ、画像データ、および追跡調査データを収集した。TFNEを、主に陽性の症状（前兆様の伝播性感覚障害、陽性視覚症状または四肢麻痺）と、主に陰性の症状（一過性脳虚血発作様の突然発症する四肢脱力、不全失語症、または視覚失調）に分けた。我々の結果と、既報の系統的レビューで同定されたすべての症例を統合した。

結果：この多施設共同コホートにおいて、25例の患者（14.5%：95%信頼区間、9.6%～20.7%）にTFNEが認められた。陽性症状と陰性症状の同程度によくみられた（それぞれ52%および48%）。最も多くみられた神経画像の特徴は、白質希薄化（84%）、葉性ICH（76%）、多発性脳葉微小出血（58%）、および脳表（皮質）ヘモジデリン沈着症／円面発黒も脳下出血（54%）であった。TFNEを有するCAA患者では、他の画像上の特徴は見られなかったが、TFNEを有さない患者と比べて脳表（皮質）ヘモジデリン沈着症／円面発黒も脳下出血の頻度が高かった（50%対19%：p=0.001）。中央値14カ月の期間中、TFNE患者の50%に症候性の葉性ICHが生じた。メタ解析の結果、8週間のTFNEの症候性ICHのリスクは24.5%（95%信頼区間、15.8%～36.9%）であり、これは臨床的特徴や過去の症候性ICHと関連がなかった。

結論：TFNEはCAAにおいてよくみられ、陽性と陰性の両方の神経学的症候が含まれ、脳表（皮質）ヘモジデリン沈着症／円面発黒も脳下出血に起因する可能性がある。TFNEは予防できる可能性のある症候性ICHの高い早期リスクを予測する。このようなエピソードの検査においては血液に敏感な磁気共鳴画像シーケンスが重要である。

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