Cerebral Microbleeds and Cortical Superficial Siderosis in Patients Presenting With Minor Cerebrovascular Events

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Background and Purpose—Transient focal neurological episodes occur in cerebral amyloid angiopathy (CAA) and can mimic transient ischemic attack (TIA). Risk factors for outcomes of minor ischemic stroke or TIA might differ in patients with and without cerebral microbleeds (CMBs), including CAA-consistent lobar CMB.

Methods—Baseline magnetic resonance imaging (MRI) was analyzed for CMBs and cortical superficial siderosis in 416 patients in the prospective computed tomography and MRI in the CATCH study (Triage of TIA and Minor Cerebrovascular Events to Identify High Risk Patients). Clinical symptoms, baseline characteristics, recurrence, and 90-day modified Rankin Scale were prospectively collected. MRI white-matter hyperintensity was measured using the Fazekas scale.

Results—CMBs were detected in 65 (15.6%) and cortical superficial siderosis in 11 patients (2.6%). Lobar CMBs were present in 49 (11.8%). In multivariable logistic regression adjusted for risk factors and age, subcortical Fazekas score was associated with lobar CMB (odds ratio, 2.07; 95% confidence interval, 1.23–3.48; P=0.006). Forty-two patients (10.1%) had lobar-only CMBs with or without cortical superficial siderosis consistent with modified Boston criteria for possible/probable CAA. The possible/probable CAA pattern was not predictive of recurrent TIA (odds ratio, 0.42; 95% confidence interval, 0.05–3.31; P=0.41), stroke (odds ratio, 1.24; 95% confidence interval, 0.26–5.99; P=0.79), or 90-day modified Rankin Scale score ≥2 (odds ratio, 1.38; 95% confidence interval, 0.62–3.07; P=0.42).

Conclusions—CMBs in TIA and minor stroke are moderately common but do not predict recurrence or 90-day outcome. CAA-related transient focal neurological episodes and TIA have overlapping clinical symptoms, suggesting that MRI may be needed for differentiation. (Stroke. 2016;47:2236-2241. DOI: 10.1161/STROKEAHA.116.013418.)

Key Words: amyloid angiopathy ▪ magnetic resonance imaging ▪ siderosis ▪ transient ischemic attack

We sought to assess the prevalence and risk factors of patients with cerebral microbleeds (CMBs) and cortical superficial siderosis and classify their pattern in a cohort presenting with TIA and minor cerebrovascular events. We hypothesized that patients with CMBs would be older and have a higher prevalence of hypertension and other vascular risk factors and that patients with CMBs and superficial siderosis consistent with a probable CAA pattern would be more likely to have recurrent events within 90 days.

Methods

We analyzed patients of the previously published computed tomography (CT) and magnetic resonance imaging (MRI) in the CATCH study (Triage of TIA and Minor Cerebrovascular Events to Identify High Risk Patients). In this prospective longitudinal cohort study, patients aged at least 18 years presenting with a high-risk TIA of focal weakness and speech disturbance (lasting ≥5 minutes) or minor ischemic stroke (National Institute of Health Stroke Scale score, ≤3)
who were referred to the stroke team at Foothills Medical Centre, Calgary, were approached for enrollment. Patients were examined by a stroke neurologist and had a CT with angiography and MRI completed. Exclusion criteria included premorbid modified Rankin Scale (mRS) score ≥2, acute treatment with a thrombolytic drug, or a serious comorbid illness that would likely result in death within 3 months. The local institutional ethics committee approved this protocol, and patients provided written informed consent. Detailed baseline clinical and outcome information were prospectively collected for each patient. Baseline clinical information included age, sex, hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, current or past smoking, pre-event antiplatelet drug use, pre-event anticoagulant drug use, presenting symptoms, and if symptoms were ongoing at the time of presentation and National Institute of Health Stroke Scale score.

Baseline Imaging
At our center, CT with angiography is standard of care for all patients presenting with recent TIA within 24 hours. MRI was performed in consecutive patients as mandated by the CATCH study protocol.

MRIs were completed on either a General Electric 3-T scanner or a Siemens 1.5-T MR scanner. Sequences included diffusion-weighted image (DWI), apparent diffusion coefficient, fluid attenuation inversion recovery, and T2*-weighted gradient-echo (GRE); sequence parameters are provided in Table 1 in the online-only Data Supplement. All imaging was assessed by a neurologist who remained blinded to the results of the other imaging modality (CT and CT with angiography) and clinical symptoms. The presence, number, and location of CMB were read on T2*-GRE images according to Standards for Reporting Vascular Changes on Neuroimaging consensus and documented using a standardized case report form modified from the validated Brain Observer MicroBleed Scale, which has been used in other multicenter studies in healthy and disease populations.5,6 The presence and number of sulci affected by cortical superficial siderosis were also documented. The pattern of CMBs and siderosis was assessed for possible or probable CAA defined by modified Boston criteria.7 White-matter hyperintensities of presumed vascular origin (white-matter hyperintensities) were read on fluid attenuation inversion recovery sequence according to Fazekas scale.8 Acute infarction was inferred when hypointense lesions were present on DWI. Follow-up MRI was acquired at 90 days.

Patient Outcomes
Patients whose symptoms resolved within 24 hours of onset were classified as TIA; those with symptoms persisting >24 hours, even if minor, were classified as ischemic stroke.9 At the time of the 90-day follow-up, the treating physician rated mRS and recurrent TIA/stroke. Recurrent stroke was defined as a functional deterioration in neurological status of vascular origin lasting 24 hours or a new sudden focal neurological deficit of vascular origin lasting >24 hours (that was not felt to be secondary to other nonvascular factors: drugs, fever, and infection) adjudicated by 2 senior neurologists.10 Recurrence types were ischemic stroke and hemorrhagic stroke.

Clinical Information
Clinical information was collected by stroke neurologists and stroke fellows who were certified in mRS and National Institute of Health Stroke Scale assessment and were trained in filling in the case report forms. In addition to the already available presenting symptoms (hemineglect, monocular vision loss, hemianopsia, diplopia, speech alteration, weakness, sensory symptoms, and ataxia) and their duration (ongoing at the time of presentation or not, lasting more or less than 24 hours), we retrospectively reviewed the charts of patients with CMBs in a probable CAA pattern to analyze possible specific features of their presenting symptoms. In conjunction with their imaging findings, 2 investigators (C.Z. and E.E.S.) came to a consensus whether the presenting symptoms were more likely caused by probable CAA or ischemic cerebrovascular disease.

Statistical Analysis
Measures of central tendency and measures of variability were used according to standard descriptive statistics. We additionally developed multivariable logistic regression models to test the association between risk factors and CMB/cortical superficial siderosis and the patient’s outcome. We included available variables that were deemed clinically relevant a priori and have been investigated in previous studies.11,12 Statistical analysis was performed using STATA software (Stata 14; Stata Corp, College Station, TX).

Results
T2* GRE images were available for 431 of 510 patients (84.5%). Fifteen had to be excluded for poor quality, leaving 416 of 510 (81.6%) for analysis. Seventy-five patients were scanned on the 1.5-T scanner and 341 on the 3-T scanner. Baseline characteristics and outcomes for patients with and without MRI available are compared in Table 1. More than half (243/416; 58.4%) of patients had evidence of acute brain infarction on MRI DWI. The median time to MRI was 17.3 hours (25%–75% confidence interval [CI], 10.3–22.4).

Sixty-five patients (15.6%) had at least 1 CMB. The detection rate was not significantly different at 3 T (55/341; 16.1%) compared with 1.5 T (10/75; 13.3%; P=0.55). The median number of CMB was 1 with an interquartile range of 1 and a total range of 33. Forty-nine (74.4%) of those patients had CMB in a lobar brain region (median, 1; interquartile range, 1; range, 25), 16 (24.6%) in a deep brain region (median, 1; interquartile range, 1; range, 24), and 10 (15.4%) in the cerebellum (median, 1; interquartile range, 0.5; range, 1). The total adds to >65 because 11 patients had CMBS in >1 region: 7 had lobar and deep CMBS, 3 had lobar and cerebellar CMBS, and 1 had...
Table 2. Baseline Characteristics of Patients With and Without Cerebral Microbleeds

<table>
<thead>
<tr>
<th></th>
<th>CMB Positive, (n=65)</th>
<th>CMB Negative, (n=351)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (IQR)</td>
<td>76 (15)</td>
<td>66 (22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>37 (57)</td>
<td>189 (53.8)</td>
<td>0.21</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>1 (1.5)</td>
<td>2 (0.6)</td>
<td>0.40</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>5 (7.7)</td>
<td>22 (6.3)</td>
<td>0.78</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>7 (10.8)</td>
<td>49 (14)</td>
<td>0.48</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>11 (16.9)</td>
<td>55 (15.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Past smoking, n (%)</td>
<td>15 (23.1)</td>
<td>75 (21.4)</td>
<td>0.09</td>
</tr>
<tr>
<td>Aspirin use, n (%)</td>
<td>24 (36.9)</td>
<td>111 (31.6)</td>
<td>0.70</td>
</tr>
<tr>
<td>Plavix use, n (%)</td>
<td>4 (6.2)</td>
<td>19 (5.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Warfarin use, n (%)</td>
<td>3 (4.6)</td>
<td>13 (5.7)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

\(P\) value: t test, chi-square test, or Fisher exact test as appropriate. CMB indicates cerebral microbleed; and IQR, interquartile range.
During review, consensus was reached that 4 (31%) of 13 patients’ symptoms were more likely caused by CAA rather than ischemic cerebrovascular disease. They were 2 patients with persistent symptoms and negative DWI, 1 patient with transient symptoms and negative DWI, and 1 patient with transient symptoms and a small DWI lesion which could have been caused by CAA, respectively.

Discussion

Our study showed that CMBs are moderately common in TIA and patients with minor cerebrovascular events but do not strongly predict clinical recurrence or 90-day functional outcome. We found that 3.1% of minor stroke and TIA patients had a pattern of lobar CMBs and siderosis consistent with probable CAA; when restricted to TIA only, 1.9% had a probable CAA pattern.

The prevalence of CMB in minor ischemic stroke and TIA (15.6%) was higher in our study than in the population-based Framingham study (8.8%) but lower than in the population-based Rotterdam study (18.7%), which used a higher sensitivity GRE sequence than the conventional GRE sequences used in our study.13,14 Studies of ischemic stroke have reported CMB prevalence of 8.9% to 44%.15,16 However, there are a paucity of studies that have reported CMB prevalence in TIA.17 Population-based studies have identified age, hypertension, and diabetes mellitus as risk factors for CMBs. However, in our study population at high vascular risk, we did not find associations between collected cardiovascular risk factors at baseline and CMBs. We found that higher Fazekas score was associated with CMB and a higher subcortical Fazekas score predicted lobar CMB. Correlations between leukoaraiosis and CMB have been reported previously.18

Cortical superficial siderosis was detected in 11 (2.6%) of our patients. To our knowledge, this study is the first to report on the prevalence of siderosis in a consecutive cohort of minor stroke and high-risk TIA patients. This prevalence was higher than that in the general population (0.7%) but lower than in patients with cognitive impairment (6.1%) and patients with ICH because of probable CAA (≈40%).19–22 CAA is proposed to be a cause of TFNE, which mimics the symptoms of TIA but is associated with high hemorrhage risk rather than the risk of recurrent ischemic stroke. Therefore, recognizing this syndrome is important to avoid escalating antithrombotic treatment in patients at a risk of hemorrhage. To our knowledge, this study is the first to report on patterns of CMBs and cortical superficial siderosis which are consistent versus not consistent with CAA in a consecutive series of minor stroke and high-risk TIA patients. Overall, a probable CAA pattern was uncommon (3.1%). Among patients with TIA and not clinical stroke, the prevalence of a probable CAA pattern was 1.9%. On the basis of the 95% confidence limits around these estimates, TFNE caused by CAA could account for ≤5% of patients with high-risk TIA symptoms seen in an emergency department.

Many patients with the probable CAA pattern had DWI lesions that suggested large arterial infarction, possibly from an embolic source, indicating the use of DWI to identify potential causes of minor stroke and transient symptoms and suggesting the need for consideration of workup of embolic sources. True probable CAA-related TFNE may have been captured in only the 2 patients with persistent symptoms and negative DWI, the 1 patient with transient symptoms and negative DWI, and the 1 patient with transient symptoms and a small DWI lesion, which could have been caused by CAA.

Possible/probable CAA in our study was not predictive of recurrent TIA or hemorrhagic/ischemic recurrent stroke. However, the single patient who had an ICH during the 90-day follow-up was a patient who presented with a stroke and had probable CAA with widespread (disseminated) cortical superficial siderosis. This highlights the need to avoid escalating antithrombotic therapy in patients with transient or minor neurological symptoms and probable CAA, unless a high-risk predisposing source to ischemic stroke is found. Other studies have found that the presence of CMB, and especially multiple CMB, was associated with an increased risk of stroke, including first-ever ischemic stroke.23,24 Presumably, the follow-up period in our study period was too short to detect an increase in stroke recurrence. Likewise, our
study follow-up was probably too short to detect new incidental CMBs, as we did not find any new CMB at 90 days on follow-up MRI scan. A population-based study in Iceland however found that 18.4% subjects developed new CMBs in 5 years. It might therefore be of interest to follow up a patient cohort like ours for a longer period of time.

Previous antiplatelet or anticoagulation therapy in our study was not associated with the presence of either CMB or cortical superficial siderosis. However, heparins, warfarin, newer anticoagulants, and antiplatelet agents all convey a potential risk of bleeding, especially in patients whose hypertension is not well controlled. There is a potential risk of hemorrhagic stroke when patients with CMB or cortical superficial siderosis are treated with these medications. One of the patients in our study with probable CAA-related TFNE developed a large lobar ICH when treated with aspirin. More data are needed to quantify the risk of antiplatelets versus anticoagulants for both short-term use and long-term treatment in patients with CMBs, and future studies should address this pressing clinical issue.

The predominantly negative symptoms at clinical presentation are in part reflective of the CATCH study inclusion criteria which required high-risk symptoms, defined as speech and motor impairment longer than 5 minutes. Interestingly, 3 patients had fluctuating symptoms/repetitive episodes before the index event, which is a described feature of TFNE. None of those patients had ischemic lesions on DWI. Although CAA-related TFNEs were initially thought to mostly cause sensory symptoms, newer research suggests that negative symptoms, such as weakness, are actually more common. Although thin-sliced CT is a valuable emergency diagnostic tool to rule out intracranial hemorrhage and cortical superficial siderosis if immediate MRI is not available, it is not sensitive enough to detect CMB.

Strengths of our study are the prospective data acquisition and enrollment of a typical patient cohort presenting emergently with minor ischemic stroke and TIA symptoms. Limitations include the relatively few number of patients with CMB and a short follow-up period. The generalizability of our findings to other centers and practice settings is unknown. Twenty percent of our patients did not undergo baseline MRI; however, this was because of scheduling issues and availability of the MRI scanner and is therefore not connected to our primary study question. By design, the CATCH study did not include patients with acute subarachnoid hemorrhage or without motor or speech symptoms; therefore, our findings may not be generalizable to those types of patients.

Conclusions

CMBs in TIA and minor stroke patients are moderately common but do not strongly predict clinical recurrence and or 90-day functional outcome. Clinical presentations for CAA-related TFNE and TIA might be overlapping, suggesting that MRI may be needed to differentiate them. Larger prospective studies with longer follow-up periods are needed to determine the use and cost-effectiveness of MRI in patients with transient neurological events.

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Disclosures

None.

References


