

# Cerebral Amyloid Angiopathy–Related Transient Focal Neurologic Episodes

Eric E. Smith, MD, MPH, Andreas Charidimou, MD, PhD, Cenk Ayata, MD, David J. Werring, MD, and Steven M. Greenberg, MD, PhD

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## Correspondence

Dr. Smith  
eesmith@ucalgary.ca

## Abstract

Transient focal neurologic episodes (TFNEs) are brief disturbances in motor, somatosensory, visual, or language functions that can occur in patients with cerebral amyloid angiopathy (CAA) and may be difficult to distinguish from TIAs or other transient neurologic syndromes. They herald a high rate of future lobar intracerebral hemorrhage, making it imperative to differentiate them from TIAs to avoid potentially dangerous use of antithrombotic drugs. Cortical spreading depression or depolarization triggered by acute or chronic superficial brain bleeding, a contributor to brain injury in other neurologic diseases, may be the underlying mechanism. This review discusses diagnosis, pathophysiology, and management of CAA-related TFNEs.

## Introduction

Cerebral amyloid angiopathy (CAA) is a disease of the small arteries and arterioles that predominantly affects the cortex and leptomeninges.<sup>1</sup> Age-related sporadic CAA is caused by deposition of  $\beta$ -amyloid (A $\beta$ ), while rare genetic forms of the disease can be caused by deposition of A $\beta$  or other amyloid proteins. This amyloid deposition damages the vessel wall, leading to thickening, hyalinization, and smooth muscle cell loss, ultimately leading to parenchymal brain injury due to both bleeding and ischemia.<sup>1</sup>

Originally recognized primarily as a cause of lobar intracerebral hemorrhage (ICH), recent research shows that CAA also causes convexity subarachnoid hemorrhage (cSAH) and transient neurologic symptoms.<sup>2,3</sup> These consist of short (typically under 30 minutes), frequently recurrent stereotyped episodes of focal (usually sensory or motor) disturbances, often exhibiting a spreading progression, where the symptoms smoothly migrate over minutes to adjacent body parts as represented in the cerebral cortex (e.g., from the hand up the arm into the face).<sup>4,5</sup> The difficulty in clinical diagnosis is that similar symptoms occur in other conditions such as TIA, migraine with aura, or seizures. Various terms have been used to describe this syndrome, including “amyloid spells.”<sup>6</sup> We recommend the term CAA-related transient focal neurologic episodes (CAA-related TFNEs)<sup>5</sup> to distinguish the transient neurologic symptoms seen in CAA from other causes of temporary neurologic disturbances and to avoid the nonspecific term spells.

Recognizing CAA-related TFNEs is important. Patients with CAA-related TFNE are at substantial risk of subsequent lobar ICH<sup>5</sup> that would be exacerbated by inappropriate prescription of antithrombotics for a presumed TIA diagnosis. The high observed rates of ICH following TFNE raise the question whether the mechanisms underlying TFNE also predispose to future neuropathologic events such as vascular rupture or neuronal injury.

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From the Department of Clinical Neurosciences (E.E.S.), Hotchkiss Brain Institute, University of Calgary, Canada; Hemorrhagic Stroke Research Program (A.C., S.M.G.), Department of Neurology, Massachusetts General Hospital Stroke Research Center, Harvard Medical School; Stroke Service and Neurovascular Research Lab (C.A.), Department of Neurology, Massachusetts General Hospital, Boston; and Stroke Research Centre (D.J.W.), University College London Queen Square Institute of Neurology, UK.

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## Glossary

A $\beta$  =  $\beta$ -amyloid; CAA = cerebral amyloid angiopathy; CI = confidence interval; cSAH = convexity subarachnoid hemorrhage; CSD = cortical spreading depolarization; cSS = cortical superficial siderosis; DWI = diffusion-weighted imaging; ICH = intracerebral hemorrhage; SAH = subarachnoid hemorrhage; TFNE = transient focal neurologic episode.

This review synthesizes information on the clinical and neuroimaging features, pathophysiology, diagnosis, prognosis, and management of CAA-related TFNE.

## Methods

This narrative review was informed by a systematic search of the PubMed database on November 8, 2020, using the terms cerebral amyloid angiopathy or caa or “cerebral amyloid angiopathy” (MeSH) and transient or TFNE or transient ischemic attack or TIA or subarachnoid hemorrhage (text word) or siderosis (text word) or subarachnoid hemorrhage or “amyloid” (MeSH) or amyloid and spells or spell. The search returned 437 articles, of which 173 were related to the topic and reviewed in full. Hand-searching identified 4 additional articles.

## Clinical Presentation

CAA-related TFNEs were sporadically reported as early as the 1980s.<sup>7</sup> An early case series identified a characteristic spread of symptoms into contiguous body areas and evidence of small hemorrhagic lesions or subsequent large ICH in cortical locations corresponding to the neurologic symptoms.<sup>8</sup>

The increasing awareness of CAA as a clinical and pathologic entity, and the more widespread availability of blood-sensitive MRI sequences that allow diagnosis by application of the Boston criteria,<sup>9,10</sup> have increased our understanding and recognition of CAA-related TFNEs.<sup>8,11,12</sup> In a European multicenter retrospective cohort study of 172 patients with CAA based on the Boston criteria,<sup>5</sup> TFNEs were the most common clinical presentation of CAA after lobar ICH, being present in 14.5%. TFNE clinical phenomenology was classified into 2 groups: predominantly positive or predominantly negative symptoms, each being equally common (52% vs 48%, respectively), with 25% having both positive and negative symptoms. The commonest positive symptom consisted of transient paresthesias in the mouth or hand (32%), often but not always with a gradual spread to contiguous body parts. The negative symptoms included focal weakness and dysphasia. A minority (<20%) had limb-jerking episodes or transient visual disturbances involving blurred vision or visual loss, flickering, or flashing lights and transient zig-zags (teichopsia). Most participants (68%) had multiple episodes, nearly always stereotyped (i.e., recurrent episodes similar or identical to the initial presentation). TFNEs lasted <6 minutes in 44% of patients, <30 minutes in 70%, and  $\leq$ 3 hours in 96%. A subsequent systematic review<sup>13</sup> confirmed a high frequency of positive spreading sensory symptoms (about

80%) but also predominantly negative symptoms (such as hemiparesis or nonfluent dysphasia) in around 40%.

## Neuroimaging

CAA-related TFNEs are closely, but not exclusively, associated with convexity subarachnoid hemorrhage (cSAH) or cortical superficial siderosis (cSS) (figure 1), implicating superficial bleeding in the pathophysiology of this condition.<sup>14</sup> Two cohort studies showed that the majority of patients with CAA-related TFNEs (first ever or recurrent) have 1 or both of cSAH or cSS (58%<sup>5</sup> and 83%,<sup>13</sup> respectively). Disseminated cSS is much more common in patients with CAA presenting with TFNEs than patients with CAA presenting with ICH.<sup>15,16</sup>

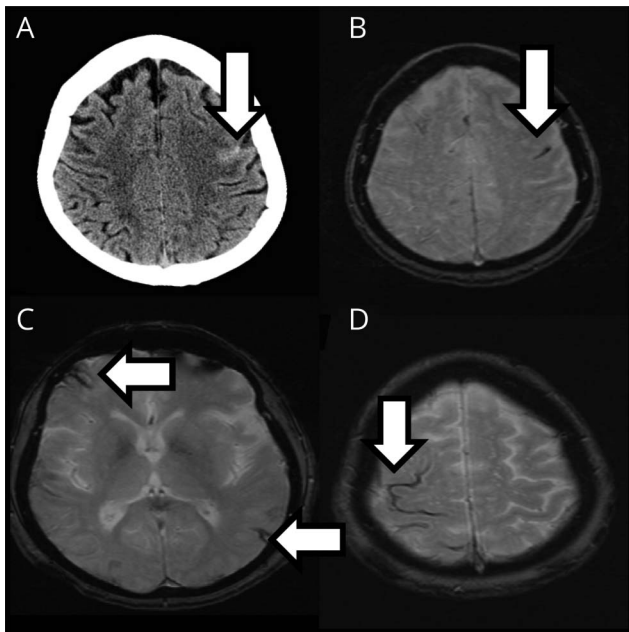
## Pathophysiology

The slow spreading pattern of signs and symptoms congruent with cortical somatotopy, the preponderance of mixed positive and negative symptoms, and the transient and often stereotypic nature are the most conspicuous features of CAA-related TFNEs. These characteristics implicate the phenomenon of cortical spreading depolarization (CSD), also known as spreading depression, in response to superficial hemorrhagic lesions.

CSD is an electrophysiologic phenomenon associated with near complete depolarization of virtually all cell types in the brain tissue including neurons, glia, possibly perivascular nerves, and the vasculature.<sup>17</sup> The sustained loss of neuronal membrane potentials and changes in neurochemical milieu preclude synaptic transmission and action potentials for minutes. As a result, there is complete electrophysiologic silence during CSD, which distinguishes CSD from seizures. The depolarization of CSD slowly propagates (a few millimeters per minute) by way of chemical contiguity, often for many centimeters across contiguous cortical regions, explaining the slow, smooth, somatotopic spread of neurologic deficits that is virtually pathognomonic for CSD. The cardinal features of CAA-related TFNEs, such as the marching pattern, positive and negative stereotypic symptomatology, and complete reversibility, strongly support CSD as the underlying mechanism, even though direct electrophysiologic evidence is lacking and may be impractical to acquire, as this would require invasive placement of subdural or depth electrodes.

The congruence between location of cSAH or cSS and the somatotopy of neurologic deficits (most often central sulcal cSAH and contralateral somatosensory migrating symptoms<sup>13</sup>) suggests that CSDs are triggered from these CAA lesions (figure 2). In the absence of direct mechanistic data, however, we can only speculate on what triggers CSD in CAA. CSDs can be triggered by hemorrhage, as described in the setting of

**Figure 1** Convexity Sulcal Subarachnoid Hemorrhage (cSAH) and Cortical Superficial Siderosis (cSS)



A 71-year-old woman presented with paresthesias and weakness of the right hand. (A) CT showed acute cSAH in a left frontal sulcus, visible as a linear hypointensity on T2\*-weighted gradient-recalled echo (GRE) MRI (B). MRI GRE also showed 3 areas of cSS (arrows, C and D) in sulci without acute cSAH. One year later, the patient had a left parietal lobar intracerebral hemorrhage.

ICH<sup>18</sup> and aneurysmal subarachnoid hemorrhage (SAH).<sup>19</sup> However, experimental data show that simple cortical exposure to whole blood does not trigger a CSD.<sup>20</sup> In contrast, hemolyzed blood is a potent CSD trigger, presumably due to its high potassium (K<sup>+</sup>) content. This raises the interesting possibility that SAH trapped in a cortical sulcus acts as a persistent source of blood breakdown products, including K<sup>+</sup>, leading to recurrent, stereotyped CSD events that gradually diminish in frequency as the depolarizing substances are slowly cleared.<sup>21</sup> Sulcal SAH could also facilitate CSD occurrence by exerting local mechanical pressure on adjacent cortex and by causing cortical arterial or venous thrombosis, both of which are known CSD triggers. Indeed, 2 case series show that sulcal SAH had adjacent cortical DWI lesions in about half of the cases.<sup>22,23</sup> Mechanical pressure might be a CSD trigger in the setting of cortical microbleeds. However, the presence of locally elevated pressure adjacent to sulcal SAH or microbleeds has not been directly measured, and it would be technically difficult to do so. One final potential mechanism triggering CSD may be vasospasm caused by cSAH in the setting of CAA. However, this is less likely because vasospasm is a slower and more lasting event than TFNE; moreover, convexity and sulcal SAH are frequent after trauma, but do not lead to clinically relevant vasospasm or TFNEs.

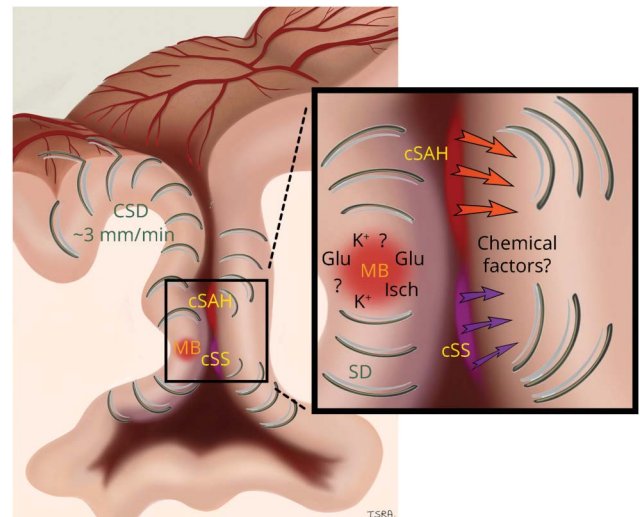
None of the abovementioned mechanisms directly related to SAH explains the apparent association between TFNEs and cSS without acute cSAH. Hemosiderin by itself has not been

shown to trigger or facilitate CSDs, and any gliosis associated with cSS would be expected to suppress rather than facilitate CSD susceptibility.<sup>24</sup> Seizure activity could trigger a CSD,<sup>25</sup> which could help terminate the seizure but itself propagate in the tissue creating the TFNE. Whereas epileptic events have not been observed on routine electrophysiologic studies in patients with CAA with TFNEs,<sup>13,26,27</sup> including in 1 patient with 2 episodes while undergoing continuous EEG,<sup>28</sup> surface EEG is not highly sensitive for detecting focal seizures.

Another potential trigger for CSD is cerebral ischemia.<sup>17,29</sup> Although CAA is primarily recognized as a disease characterized by hemorrhages, focal cerebral ischemia is common as well. Therefore, it is possible that recurrent ischemic events due to diseased cortical arterioles trigger recurrent stereotypic CSD events, and some eventually lead to cortical infarcts visible on DWI close to cSAH in CAA.<sup>22,23,30</sup>

CSDs dramatically increase oxygen and glucose consumption in brain tissue, disrupt the blood–brain barrier for more than 24 hours, induce vasoconstriction, and upregulate matrix metalloproteinase and proinflammatory cytokine expression.<sup>31–33</sup> Despite all these changes, CSD is not by itself injurious to the brain tissue unless metabolically compromised. Indeed, numerous CSDs can occur in otherwise normal tissue without causing any cell death. However, in brains with CAA (and often coexisting Alzheimer disease pathology), these changes could have complex

**Figure 2** Possible Mechanisms Triggering Spreading Depolarizations



Schematic representation of hypotheses on the origin of spreading cortical depolarizations (CSDs) within a sulcus affected by cerebral amyloid angiopathy (CAA). Convexity subarachnoid hemorrhage (cSAH) and cortical superficial siderosis (cSS) could trigger CSD by releasing chemical factors that affect the brain tissue or pial vasculature. An acute cortical microbleed might also trigger CSD via ischemia (Isch) in the territory of the ruptured artery, via mechanical distortion of brain tissue by expanding microbleed, or by release of depolarizing factors from plasma leakage or hematoma lysis (e.g., potassium [K<sup>+</sup>] ions or glutamate [Glu]). Once initiated, CSDs propagate in cortical gray matter at a speed of ~3 mm/min for many centimeters, creating a TFNE.



adverse effects on neurovascular structure and function, although it remains speculative whether TFNEs alter the disease course.

## Diagnosis

The diagnosis relies on recognizing a compatible clinical syndrome accompanied by clinical, neuroimaging, or neuropathologic evidence of CAA and the absence of a more plausible alternative cause. TIA, migraine aura, and focal seizures are the most common alternative diagnoses to CAA-related TFNEs based on clinical symptoms prior to neuroimaging (table 1). Compared to TIA, CAA-related TFNEs are more likely to exhibit migratory spread, affect sensation, and recur in a stereotyped manner.<sup>34</sup> Diagnostic characteristics of CAA-related TFNEs are shown in table 2.

Two cohort studies have defined operational criteria for identifying CAA-related TFNEs. The first of these articles defined CAA-related TFNE as “a clearly documented history of transient ( $\leq 24$  hours), fully resolving, focal neurologic episodes accompanied by evidence of possible, probable, or definite CAA according to the Boston criteria, and no known alternative explanation other than CAA (e.g., structural brain lesion, atrial fibrillation, extracranial or intracranial stenosis).”<sup>5</sup> Another article defined TFNEs as “a clinical episode of transient focal neurologic symptoms including numbness/tingling, weakness, dysarthria or aphasia lasting minutes to 1 hour with subsequent complete resolution.”<sup>13</sup>

The validated Boston criteria should be applied to infer the presence of moderate to severe CAA.<sup>9</sup> In 2010, the criteria were modified to include cSS as equivalent to a lobar hemorrhage or microbleed.<sup>10</sup> The Boston criteria have been validated pathologically in patients with lobar ICH<sup>9</sup> but there are few pathology data available in patients with CAA-related TFNEs, because unlike ICH they are not fatal and not treated surgically. In 1 case, a 71-year-old woman with TFNEs related to a right cSAH and a concurrent contralateral lobar ICH had evidence of vascular A $\beta$  at death, with more severe deposition in the leptomeningeal than the cortical vessels.<sup>35</sup> Another pathology-confirmed CAA case consisted of a 58-year-old man with recurrent TFNEs followed by rapid cognitive decline and death.<sup>8</sup> Indirect evidence of the validity of the

Boston criteria to diagnose CAA-related TFNEs comes from prospective cohort studies showing that patients with CAA-related TFNE have a similarly high rate of subsequent lobar ICH as patients with lobar ICH and probable CAA.<sup>5,36</sup>

Investigations should at minimum consist of a history, physical and neurologic examination, bloodwork for metabolic causes of neurologic disturbances (electrolytes, creatinine, liver function tests, and complete blood count), coagulopathies (platelet count, prothrombin time, and partial thromboplastin time), and neuroimaging. CT will identify the cases with acute cSAH. MRI with susceptibility-weighted sequences (such as T2\*-weighted gradient recalled echo or susceptibility-weighted imaging) has equivalent sensitivity to CT for SAH<sup>37</sup> and will additionally identify cSS and lobar microbleeds that can point to the presence of CAA. MRI diffusion-weighted imaging (DWI) is useful because it may identify patterns of abnormalities consistent with infarction from thromboembolism rather than CAA; however, the clinician must be aware that small DWI abnormalities frequently occur in CAA as well,<sup>38</sup> including in up to half of patients with CAA-related cSAH, usually adjacent to the acute hemorrhage<sup>22,23,30</sup> (figure 3). In the subacute period, MRI is more useful than CT because blood products may have resolved on CT while MRI will still show susceptibility changes related to prior bleeding events.

Patients with cSAH or cSS should at minimum undergo noninvasive angiography by CT or MRI to exclude distal aneurysms or vascular malformations. Invasive catheter angiography is probably not needed if there are radiologic markers meeting Boston criteria for CAA.

Although unlikely to be used in routine practice, A $\beta$  markers are usually positive in patients with CAA-related TFNEs. Small case series of patients with CAA-related TFNEs and cSAH have shown positive amyloid-PET<sup>39</sup> and low CSF A $\beta$ 1-40 and A $\beta$ 1-42.<sup>23</sup>

## Incidence of CAA-Related TFNEs

The incidence of CAA-related TFNEs in the general population is unknown, owing to general underrecognition and a lack of consensus diagnostic criteria. Among patients with acute nontraumatic cSAH, CAA was identified as the cause in a quarter to a third of patients of all ages<sup>11,40-47</sup> including 76% of persons 60 years of age or older.<sup>40,46</sup> Most of these patients with cSAH ( $\geq 75\%$ ) presented with TFNEs.<sup>15,16,22,36</sup> Similarly, another study found that CAA accounted for the majority of cSS cases in a hospital-based radiology database.<sup>48</sup> There are fewer data on the proportion of possible TIA that may instead be CAA-related TFNEs. In 1 prospective study of patients with possible ischemic symptoms who were consecutively consented to undergo MRI, 4/416 (1.0%) were retrospectively assessed as having CAA-related TFNEs.<sup>49</sup> Thus, current evidence suggests that most nontraumatic cSAH in the elderly, 3-quarters of cSS, and 1% of suspected TIA cases may be related to CAA.

**Table 1** Competing Causes of Transient Neurologic Symptoms

TIA
Migraine with aura
Focal seizure
Structural lesions (e.g., tumor, vascular malformation, subdural hematoma)
Metabolic abnormalities (e.g., hypoglycemia, hyponatremia)
Syncope or presyncope
Functional neurologic disorder

**Table 2** Diagnostic Characteristics of Cerebral Amyloid Angiopathy (CAA)-Related Transient Focal Neurologic Episodes (TFNEs)

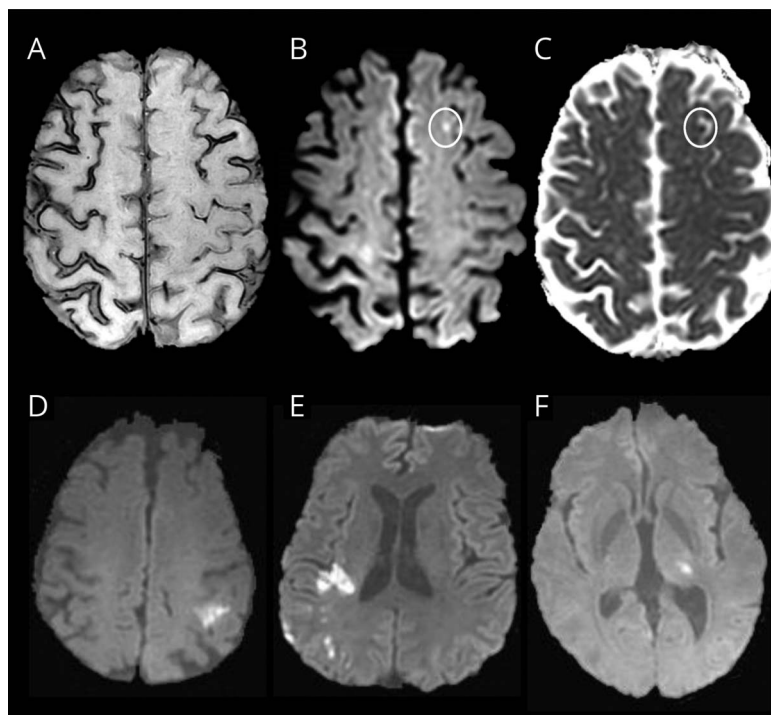
Essential
1. Transient, focal neurologic symptoms (often unilateral motor, sensory, or both, sometimes including other symptoms such as dysarthria or aphasia), usually resolving within 30 minutes (and nearly always within 3 hours); often spreading from 1 body part to another represented by contiguous cortex and often recurrent in a stereotyped or similar pattern over days or weeks
2. Neuropathologic or neuroimaging evidence of probable or possible CAA by modified Boston criteria <sup>9,10</sup>
3. Age $\geq 55$ <sup>9,10</sup>
Supportive: suggests CAA-related TFNE even when other potential causes (e.g., history of atrial fibrillation) are present
Acute convexity subarachnoid hemorrhage or cortical superficial siderosis in a sulcus adjacent to the presumed symptomatic gyrus without other identified cause
Exclusionary: suggests event was not CAA-related TFNE, even in patients with neuropathology or neuroimaging evidence of CAA
Acute infarction in a pattern consistent with thromboembolism rather than CAA; note that some patients with CAA-related TFNEs have small diffusion-weighted imaging-positive lesions near the symptomatic sulcus (figure 3)
Uncertain: features that make it unclear whether the event was a CAA-related TFNE
Competing explanations for transient event (e.g., atrial fibrillation) in the absence of supportive features of CAA-related TFNE

### Prognosis

CAA-related TFNEs herald a high risk of future symptomatic hemorrhage, both ICH and acute cSAH.<sup>4</sup> In a European multicenter study, 50% of patients with CAA-related TFNEs had symptomatic lobar ICH over a median period of 14 months.<sup>5</sup> In the same study, a systematic review and meta-analysis of all relevant case reports and case series published showed a 24.5% (95% confidence interval [CI] 15.8–36.9)

risk of symptomatic ICH at 8 weeks after TFNE, a risk uninfluenced by clinical features of the TFNE or previous symptomatic lobar ICH.<sup>5</sup> In a meta-analysis of 9 patient cohorts with acute cSAH and probable CAA, the majority of which presented with TFNEs, the ICH rate was 19% per year (95% CI 13–27).<sup>36</sup> These rates of ICH are higher than the risk of recurrent ICH after first CAA-related ICH (estimated at 7.4% per year<sup>50</sup>).

**Figure 3** MRI Diffusion-Weighted Imaging (DWI) in Cerebral Amyloid Angiopathy (CAA)-Related Transient Focal Neurologic Episodes (TFNEs) Compared With Ischemic Stroke



(A–C) From the same patient, disseminated cortical superficial siderosis (cSS) on MRI susceptibility-weighted imaging (A) with a 3 mm focus of bright signal on DWI in the left superior frontal gyrus adjacent to cSS (B, circled) with hypointensity on apparent diffusion coefficient image (C, circled), indicating restricted diffusion. Small ( $\leq 10$  mm) DWI-positive lesions are often seen in CAA with convexity subarachnoid hemorrhage and TFNEs, usually adjacent to regions of cSS and sometimes multiple.<sup>22</sup> (D–F) DWI-positive lesion patterns seen in ischemic stroke but not CAA include single larger ( $>10$  mm) DWI-positive infarcts (D), multiple DWI-positive infarcts restricted to a vascular perfusion territory (E), or DWI-positive small subcortical infarcts restricted to the territory of a single perforating artery (as in the thalamic recent subcortical infarct seen in F).

It is unclear whether this extremely high ICH risk is a direct consequence of TFNEs per se vs a consequence of the strong association of TFNEs with cSS and cSAH, which themselves predict future ICH.<sup>4,14</sup> In a cohort of 236 patients with probable CAA presenting with non-ICH neurologic symptoms (22% with TFNEs, 68% with cognitive complaints, and 10% with other symptoms), presence of cSS, especially disseminated (i.e., affecting at least 4 cortical sulci), was an independent predictor of first-ever ICH.<sup>51</sup> Additional studies<sup>52</sup> and meta-analysis<sup>53</sup> confirm that cSS is a risk factor for future ICH, independent of the number of microbleeds, in patients with CAA with or without prior history of ICH. A pooled meta-analysis of patients with cSAH found that patients fulfilling the modified Boston criteria for CAA have a high risk of future ICH: in those with probable CAA, the ICH rate per patient-year was 19% (95% CI 13–27) compared to 7% (95% CI 3–15) for those without probable CAA.<sup>36</sup> Patients with CAA who present with cSAH have at least as high a risk of future ICH as the patients who present with ICH.<sup>54</sup>

## Management

Like patients with TIA, those with TFNEs are most likely to present to a clinician after the resolution of 1 or more attacks of sensorimotor disturbance. Thus, hyperacute treatment is not usually possible or appropriate. Nevertheless, there is observational evidence that in acute cSAH there is an early risk (within 24 hours) of expansion of cSAH into the brain parenchyma as lobar ICH.<sup>35</sup> Thus, despite a lack of direct clinical trial evidence, it might therefore be reasonable to lower blood pressure in TFNEs associated with acute cSAH presenting early (e.g., within 24 hours) to a similar level to that recommended for acute ICH (below 140 mm Hg systolic).<sup>55</sup>

About 30% of patients with cSAH and TFNEs are taking antithrombotic drugs.<sup>5,13</sup> Where acute cSAH is demonstrated, it seems reasonable to withhold these drugs in the acute phase, for at least 24–48 hours given the potential for early expansion of cSAH to ICH, recurrent cSAH, or ICH. Depending on the strength of the ongoing indication for antithrombotic therapy, restarting can then be considered. As the risk of future ICH after cSAH and TFNE seems at least as high as that after ICH, it might be reasonable to avoid anticoagulant drugs for 7–8 weeks,<sup>56</sup> but controlled trials are not available. Direct oral anticoagulants consistently show a ~50% lower ICH risk than vitamin K antagonists,<sup>57</sup> so are preferred after TFNEs associated with cSAH when there is a need for oral anticoagulation. In patients with atrial fibrillation and high ischemic stroke risk, left atrial appendage occlusion is a potential option in those at very high intracranial bleeding risk on oral anticoagulation,<sup>58</sup> although the procedure does not obviate the need for postprocedure antithrombotics, at least in the short term, and randomized data are not available in patients with cSAH.

When associated with cSAH due to CAA, TFNEs often recur over a short time period,<sup>4</sup> which can cause distress for

patients. The TFNE attacks may respond to anticonvulsant drugs (e.g., levetiracetam), including those effective against migraine (e.g., topiramate),<sup>12</sup> but there are no controlled trials and the episodes may be self-limited. Patients should be reassured that although these TFNE attacks may be distressing, each attack does not usually reflect new bleeding, and the natural history is usually of improvement and remission over days to weeks.

With regard to prevention of future intracranial hemorrhage (ICH or cSAH), there are no proven interventions in CAA-related TFNE. However, given that these patients are at high risk, we suggest it would be reasonable to follow ICH guidelines for prevention, including for blood pressure control to less than 130/80 mm Hg.<sup>55</sup>

## Future Directions

CAA-related TFNEs should be suspected based on the typical clinical history of transient, often recurrent, usually spreading symptoms (suggesting CSDs), in conjunction with imaging evidence of cSAH, cSS, or microbleeds consistent with CAA. However, 2 major clinical questions surround CAA-related TFNEs. One is how to diagnose TFNEs reliably in clinical practice. A second question highlighted by the discussion of TFNE pathophysiology is whether CSD, the likely underlying mechanism for TFNEs, directly contributes to ICH risk or other types of tissue injury and thus represents a target for treatment.

One step towards improved diagnosis of CAA-related TFNEs will be to refine and validate the clinical-radiographic criteria for diagnosing CAA in patients without ICH. An international collaboration is currently underway to analyze cases with a range of CAA-like presentations (including TFNEs), available MRI scans, and neuropathology samples, with the goal of updating the Boston criteria and identifying more sensitive imaging biomarkers. Any improvements in biomarkers and diagnosis of CAA-related TFNEs would lead to reduced likelihood of misdiagnosis and mistreatment for these often complex clinical events.

The second more speculative question is whether clinical outcomes can be improved by preventing CSDs or other undefined mechanisms underlying TFNEs. One approach to this question would be to identify whether treatment with spreading depression-suppressing medications reduces risk for recurrent TFNEs as well as ICH and DWI-positive lesions on MRI. In principle, any treatment that reduces the susceptibility to CSD may suppress TFNEs, including migraine prophylactic interventions.<sup>59</sup> Additional important information would come from observational studies that characterize whether TFNEs are associated with future tissue injury (such as ICH) independent of their association with cSAH, cSS, and other known radiologic predictors of ICH in CAA, potentially implicating isolated TFNEs as the cause of



such injury. Studies in humans could be complemented by animal models of CAA-related spreading depolarization, allowing experimental testing of whether prevention of spreading depression affects the progression of other CAA-related processes such as hemorrhage, impaired vascular reactivity, and susceptibility to brain ischemia.

The minimum goal for future research on CAA-related TFNEs will be to improve the accuracy of the diagnosis and ensure correct treatment. The more ambitious goal will be to determine whether spreading depression is a rational therapeutic target in CAA, particularly in patients with TFNEs and potentially even those without clinically overt TFNEs.

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## Appendix Authors

Name	Location	Contribution
<b>Eric E. Smith, MD, MPH</b>	University of Calgary	Conceptualized the review, performed the literature search, drafted sections, collated the sections and drafted the introduction and conclusions
<b>Andreas Charidimou, MD, PhD</b>	Massachusetts General Hospital, Boston	Drafted sections, revised the manuscript for intellectual content
<b>Genk Ayata, MD</b>	Massachusetts General Hospital, Boston	Drafted sections, revised the manuscript for intellectual content
<b>David J. Werring, MD</b>	University College London; Queen Square Institute of Neurology, London	Drafted sections, revised the manuscript for intellectual content
<b>Steven M. Greenberg, MD, PhD</b>	Massachusetts General Hospital, Boston	Conceptualized the review, drafted sections, revised the manuscript for intellectual content

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