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Title: Cerebral Amyloid Angiopathy-Related Transient Focal Neurologic Episodes

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Abstract: Transient focal neurological 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 transient ischemic attacks (TIAs) or other transient neurological 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 neurological 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 affecting the cortex and leptomeninges[1]. Age-related sporadic CAA is caused by deposition of β amyloid, while rare genetic forms of the disease can be caused by deposition of β amyloid 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[1].

Originally recognized primarily as a cause of lobar intracerebral hemorrhage (ICH), recent research shows that CAA also causes convexity subarachnoid hemorrhage (cSAH) and transient neurological symptoms[2,3]. 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)[4,5]. The difficulty in clinical diagnosis is that similar symptoms occur in other conditions such as transient ischemic attack (TIA), migraine with aura, or seizures. In the past, various terms have been used to describe this syndrome including “amyloid spells”[6]. We recommend the term “CAA-related transient focal neurological episodes” (CAA-related TFNEs)[5] to distinguish the transient neurological symptoms seen in CAA from other causes of temporary neurological disturbances, and to avoid the non-specific term “spells”.

Recognizing CAA-related TFNEs is important. Patients with CAA-related TFNE are at substantial risk of subsequent lobar ICH[5] 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 neuropathological events such as vascular rupture or neuronal injury.

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 these 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 four additional articles.

Clinical Presentation

CAA-related TFNEs were sporadically reported as early as the 1980's.[7] An early case series identified a characteristic spread of symptoms into contiguous body areas and evidence of small haemorrhagic lesions or subsequent large ICH in cortical locations corresponding to the neurological symptoms.[8]

The increasing awareness of CAA as a clinical and pathological entity, and the more widespread availability of blood-sensitive MRI sequences which allow diagnosis by application of the Boston criteria[9,10] have increased our understanding and recognition of CAA-related TFNEs[8,11,12]. In a European multicentre retrospective cohort study of 172 patients with CAA based on the Boston criteria[5], TFNEs were the most common clinical presentation of CAA after lobar ICH, being present in 14.5%. TFNE clinical phenomenology was classified into two 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 paraesthesias 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 initial presentation). TFNEs lasted <6 minutes in 44% of patients, <30 minutes in 70%, and ≤3 hours in 96%. A subsequent systematic review[13] confirmed a high frequency of positive spreading sensory symptoms (about 80%) but also predominantly negative symptoms (such as hemiparesis or non-fluent 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[14]. Two cohort studies showed that the majority of patients with CAA-related TFNEs (first ever or recurrent) have one or both of cSAH or cSS (58%[5] and 83%[13], respectively). Disseminated cSS is much more common in CAA patients presenting with TFNEs than CAA patients presenting with ICH[15,16].

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. We argue that these characteristics implicate the phenomenon of cortical spreading depolarization

(CSD), also known as spreading depression, in response to superficial hemorrhagic lesions.

CSD is an electrophysiological phenomenon associated with near complete depolarization of virtually all cell types in the brain tissue including, neurons, glia, possibly perivascular nerves and even the vasculature[17]. 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 electrophysiological silence during CSD, which distinguishes CSD from seizures.. The depolarization of CSD slowly propagates (a few millimeters/minute) by way of "chemical contiguity", often for many centimeters across contiguous cortical regions, explaining the slow, smooth, somatotopic spread of neurological 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 neurological deficits (most often central sulcal cSAH and contralateral somatosensory migrating symptoms[13]) suggest that CSDs are triggered from these CAA lesions (Figure 3). 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 ICH[18] and aneurysmal SAH[19]. However, experimental data show that simple cortical exposure to whole blood does not trigger a CSD[20]. In contrast, haemolyzed blood is a potent CSD trigger, presumably due to its high potassium (K^+) content. This raises the interesting possibility that SAH trapped in a cortical sulcus acts as a persistent source of

blood breakdown products, including K^+, leading to recurrent, stereotyped CSD events that gradually diminish in frequency as the depolarizing substances are slowly cleared[21]. 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, two case series' show that sulcal SAH had adjacent cortical DWI lesions in about half of the cases[22,23]. 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 does not lead to clinically relevant vasospasm or TFNEs.

None of the abovementioned mechanisms directly related to SAH explain the apparent association between TFNEs and cSS without acute cSAH. Haemosiderin 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.[24] Seizure activity could trigger a CSD,[25] which could help terminate the seizure but itself propagate in the tissue creating the TFNE. While epileptic events have not been observed on routine electrophysiological studies in CAA patients with TFNEs[13,26,27] including in one patient with two episodes while undergoing continuous electroencephalography (EEG)[28], surface EEG is not highly sensitive for detecting focal seizures.

Another potential trigger for CSD is cerebral ischemia.[17,29] 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[22,23,30]

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 pro-inflammatory cytokine expression[31-33]. 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 AD pathology) these changes could have complex 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 neuropathological 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[34]. 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 papers defined CAA-related TFNE as “a clearly documented history of transient (≤24 hours), fully resolving, focal neurological 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)”[5]. Another paper defined TFNEs as “a

clinical episode of transient focal neurological symptoms including numbness/tingling, weakness, dysarthria or aphasia lasting minutes to one hour with subsequent complete resolution"[13].

The validated Boston criteria should be applied to infer the presence of moderate to severe CAA[9]. In 2010 the criteria were modified to included cSS as equivalent to a lobar hemorrhage or microbleed[10]. The Boston criteria have been validated pathologically in patients with lobar ICH[9] 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 one case, a 71 year old woman with TFNEs related to a right cSAH and a concurrent contralateral lobar ICH had evidence of vascular β amyloid at death, with more severe deposition in the leptomeningeal than the cortical vessels[35]. Another pathology-confirmed CAA case consisted of a 58 year old man with recurrent TFNEs followed by rapid cognitive decline and death[8]. Indirect evidence of the validity for the Boston criteria to diagnose CAA-related TFNEs come 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[5,36].

Investigations should at minimum consist of a history, physical and neurological examination, blood work for metabolic causes of neurological disturbances (electrolytes, creatinine, liver function tests, and complete blood count), coagulopathies (platelet count, prothrombin time, and partial thromboplastin time), and neuroimaging. Computed tomography (CT) will identify the cases with acute cSAH. Magnetic resonance imaging (MRI) with susceptibility-weighted sequences (such as T2*-weighted gradient recalled echo or susceptibility-weighted imaging) has equivalent sensitivity to CT for SAH[37] 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[38] including in up to half of patients with CAA-related cSAH, usually adjacent to the acute hemorrhage[22,23,30] (Figure 2). In the subacute period, MRI is more useful that 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 non-invasive angiography by CT or MRI to exclude distal aneurysms or vascular malformations. Invasive catheter angiopathy is probably not needed if there are radiological markers meeting Boston criteria for CAA.

Although unlikely to be used in routine practice, β amyloid markers are usually positive in patient with CAA-related TFNEs. Small cases series of patients with CAA-related TFNEs and cSAH have shown positive amyloid-positron emission tomography (PET)[39] and low cerebrospinal fluid Aβ1-40 and Aβ1-42[23].

Incidence of CAA-related TFNEs

The incidence of CAA-related TFNEs in the general population is unknown, owing to general under-recognition and a lack of consensus diagnostic criteria. Among patients with acute non-traumatic cSAH, CAA was identified as the cause in a quarter to a third of patients of all ages[11,40-47] including 76% of persons 60 years of age or older[40,46]. Most of these cSAH patients (≥75%) presented with TFNEs[15,22,36,48]. Similarly, another study found that CAA accounted for the majority of cSS cases in a hospital-based radiology database[49]. There are fewer data on the proportion of possible TIA that may instead be CAA-related TFNEs. In one 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[50]. Thus, current evidence

suggests that most non-traumatic cSAH in the elderly, three quarters of cSS, and 1% of suspected TIA cases may be related to CAA.

Prognosis

CAA-related TFNEs herald a high risk of future symptomatic hemorrhage, both ICH and acute cSAH.[4] In a European multicentre study, 50% of patients with CAA-related TFNEs had symptomatic lobar ICH over a median period of 14 months.[5] In the same study, a systematic review and meta-analysis of all relevant case reports and case series published showed a 24.5% (95% 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.[5] In a meta-analysis of nine 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%).[36] These rates of ICH are higher than the risk of recurrent ICH after first CAA-related ICH (estimated at 7.4% per year[51]).

It is unclear whether this extremely high ICH risk is a direct consequence of TFNEs per se versus a consequence of the strong association of TFNEs with cSS and cSAH, which themselves predict future ICH.[4,14] In a cohort of 236 patients with probable CAA presenting with non-ICH neurologic symptoms (22% with TFNEs, 68% with cognitive complaints and 10% other symptoms), presence of cSS, especially disseminated (i.e. affecting at least four cortical sulci) was an independent predictor of first-ever ICH.[52] Additional studies[53] and meta-analysis[54] 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[36]. Patients with CAA who

present with cSAH have at least as high a risk of future ICH as the patients who present with ICH[55].

Management

Like patients with TIA, those with TFNEs are most likely to present to a clinician after the resolution of one 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.[35] 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 140mm Hg systolic)[56].

About 30% of patients with cSAH and TFNEs are taking antithrombotic drugs[5,13]. 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[57], but controlled trials are not available. Direct oral anticoagulants consistently show a ~50% lower ICH risk than VKA[58], 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[59] although the procedure does not obviate the need for post-procedure antithrombotics, at least in the short term, and randomised data are not available in patients with cSAH.

When associated with cSAH due to CAA, TFNEs often recur over a short time period[4] 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)[12] 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 patients. 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[56].

Conclusion and 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, two major clinical questions still 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 SD-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[60]. 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 radiological predictors of ICH in CAA, potentially implicating isolated TFNEs as the cause of such injury. Studies in human 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.

Thus, 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 SD is a rational therapeutic target in CAA patients, particularly those with TFNEs and potentially even those without clinically overt TFNEs.

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Table 1. Competing causes of transient neurological symptoms

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

Table 2: Diagnostic characteristics of CAA-related TFNEs

Cardinal	
	1. Transient, focal neurological 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 one body part to another represented by contiguous cortex; and often recurrent in a stereotyped or similar pattern over days or weeks
	2. Neuropathological or neuroimaging evidence of Probable or Possible CAA by modified Boston criteria[9,10]
	3. Age ≥55[9,10]
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 DWI positive lesion near the symptomatic sulcus (Figure 2)
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

FIGURE LEGENDS

Figure 1 Title: Convexity sulcal subarachnoid hemorrhage (cSAH) and cortical superficial siderosis (cSS) **Legend.** A 71-year-old woman presented with paresthesias and weakness of the right hand. CT (panel A) showed acute cSAH in a left frontal sulcus, visible as a linear hypointensity on T2*-weighted gradient-recalled echo (GRE) MRI (panel B). MRI GRE also showed three areas of cSS (arrows, panels C and D) in sulci without acute cSAH. One year later the patient had a left parietal lobar ICH.

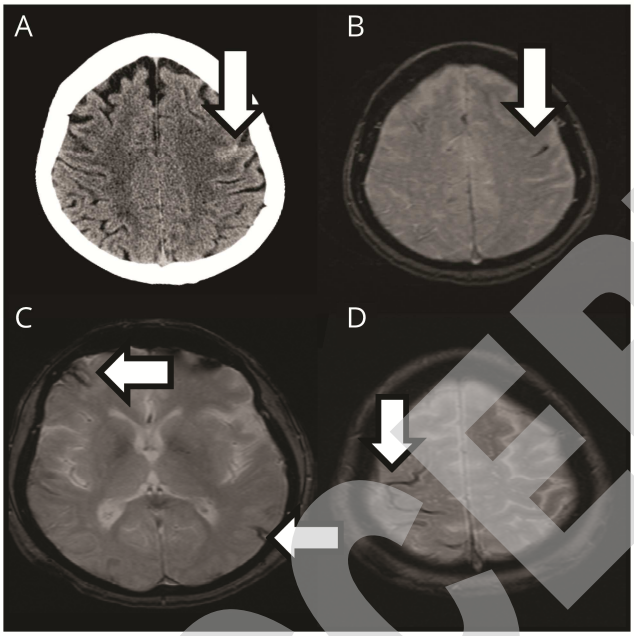


Figure 2 Title: MRI diffusion weighted imaging (DWI) in CAA-related TFNEs compared with ischemic stroke **Legend**: Panels A to C, from the same patient, demonstrate disseminated cortical superficial siderosis (cSS) on MRI susceptibility-weighted imaging (arrows, panel A) with a 3 mm focus of bright signal on DWI in the left superior frontal gyrus adjacent to cSS (panel B, circled) with hypointensity on apparent diffusion coefficient (ADC) image (panel C, circled), indicating restricted diffusion. Small (≤10 mm) DWI positive signals are often seen in CAA patients with cSAH and TFNEs, usually adjacent to regions of cSS and sometimes multiple22.). DWI positive lesion patterns seen in ischemic stroke but not CAA (D-F) include single larger

(>10 mm) DWI positive infarcts (panel D), multiple DWI positive infarcts restricted to a vascular perfusion territory (panel E), or DWI positive lacunar infarcts restricted to the territory of a single perforating artery (as in the thalamic recent subcortical infarct seen in panel F).

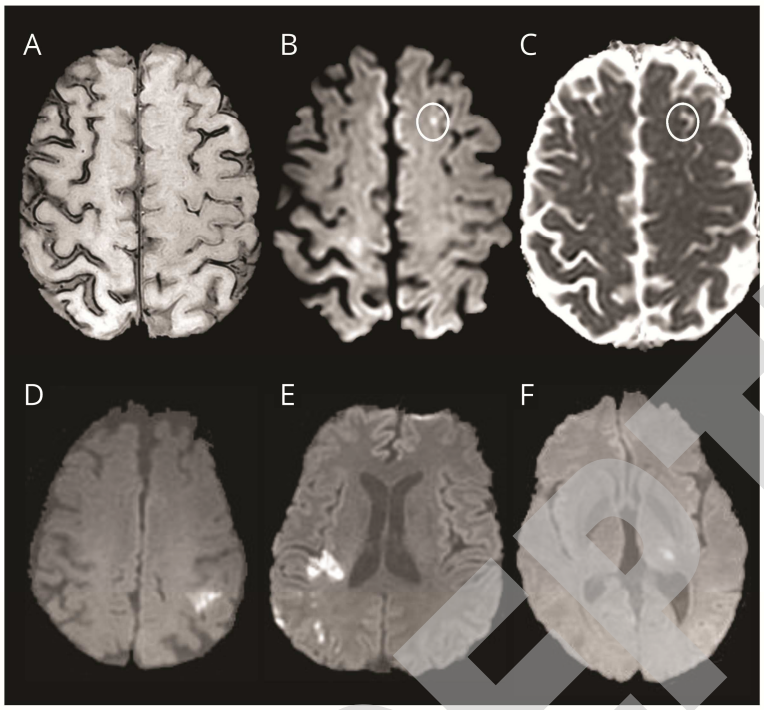
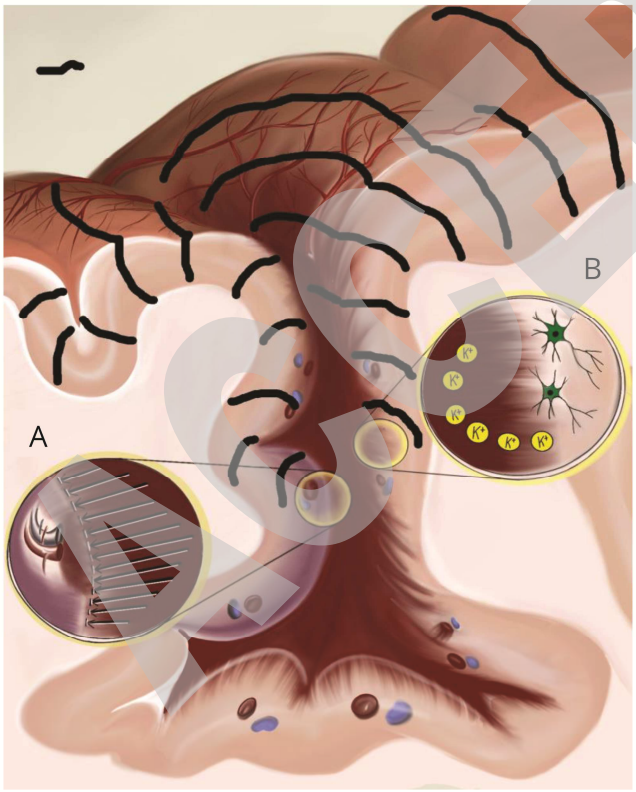


Figure 3 Title: Possible mechanisms triggering spreading depolarizations **Legend:** Schematic representation of hypotheses on the origin of spreading cortical depolarizations (CSDs) within a sulcus affected by CAA. Convexity subarachnoid hemorrhage (cSAH) and cortical superficial siderosis (cSS) could trigger CSD by releasing chemical factor(s) that affects 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, and/or by release of depolarizing factors from plasma leakage or hematoma lysis (e.g. potassium [K+] ions or glutamate [Glu]). Once initiated, CSDs propagate in cortical grey matter at a speed of ~3 mm/min for many centimeters creating a TFNE.



Appendix 1. Authors

Name	Location	Contribution
Eric Smith	University of Calgary, Calgary	Conceptualized the review; performed the literature search; drafted sections; collated the sections and drafted the introduction and conclusions.
Andreas Charidimou	Massachusetts General Hospital, Boston	Drafted sections; revised the manuscript for intellectual content.
Cenk Ayata	Massachusetts General Hospital, Boston	Drafted sections; revised the manuscript for intellectual content.
David Werring	University College London Queen Square Institute of Neurology, London	Drafted sections; revised the manuscript for intellectual content.
Steven Greenberg	Massachusetts General Hospital, Boston	Conceptualized the review; drafted sections; revised the manuscript for intellectual content.

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