

TIA-like presentations of cerebral amyloid angiopathy

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Abstract

Transient focal neurological episodes (TFNEs) are transient ischemic attack (TIA)-like episodes that may occur in patients with cerebral amyloid angiopathy (CAA). The duration of TFNEs is typically similar to TIAs with most symptoms resolving in minutes. Symptoms, similar to those of TIAs include sensory or visual disturbances, motor weakness and language impairment and there may be limb jerking or associated headache. TFNEs have a more gradual onset and tend to spread slowly to contiguous body parts like a migraine aura. TFNEs may occur repeatedly throughout the day and attacks may continue over several months. TFNEs are typically associated with focal cortical subarachnoid hemorrhage or with focal cortical superficial siderosis. They may also be seen in patients with CAA-related lobar hemorrhage, microhemorrhage or leukoencephalopathy. Migraine prophylactic agents such as verapamil and topiramate may be useful in stopping frequent recurrent TFNEs. TFNEs are an under-recognized cause of apparent TIAs. It is important to keep TFNEs in the differential diagnosis when a patient presents with a presumed TIA as thrombolysis or anticoagulation is relatively contraindicated in CAA. Gradient echo MRI should be performed to exclude microhemorrhages when TFNEs are suspected.

Clinicians most frequently associate cerebral amyloid angiopathy (CAA) with intracerebral hemorrhage or with a clinical picture of vascular cognitive impairment.¹ There have however, been increasing clinical reports documenting that CAA may cause a variety of acute clinical neurological manifestations.² Although these phenomena are superficially similar to TIAs and may be mistaken for them, they have clinical time profiles and progressions that can distinguish them from TIAs clinically. They appear to be caused by different manifestations of the complications of CAA and are now known as transient focal neurological episodes (TFNE).²⁻³

CAA frequency increases with age with approximately 50 % of individuals over the age of 75 being affected. The exact cause of CAA remains uncertain however increased production and/or decreased breakdown of amyloid proteins may have a role. CAA predominantly affects occipital regions of the brain followed by frontal and temporal areas. Cerebellar vessels are less commonly affected.³ The Boston criteria is the current standard criteria for diagnosis of CAA. In this review, we attempt to classify and describe the different causes of TFNE's in CAA.

Clinical Manifestations of TFNEs

TFNE's include all neurological phenomena that may be otherwise attributed to TIA's as well as other atypical symptoms that are specific to TFNE's.¹ The duration of TFNE's is quite similar to TIA's with most symptoms resolving before 24 hours. Some cases of TFNE's have been reported to occur for longer but resolve eventually unlike major cerebrovascular accidents. Symptoms similar to those of TIA's include sensory disturbances, motor weakness, visual disturbances and language impairment. Atypical symptoms include associated headache and focal jerking²⁻³

TFNE's vary from TIA's in that symptoms often spread to contiguous body parts much like migraine attacks.³ TFNE's also have a more gradual

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onset unlike TIA's which often have an abrupt onset. TFNE's are also more likely to occur multiple times during the day unlike TIA's which usually happen in single episodes or if multiple usually days apart.^{2,3} TFNEs may occur repeatedly over several months and be a very intrusive symptom for the patient.²⁵ The typical presentation of a TFNE is of paresthesias involving one or more limbs that spread gradually to involve contiguous areas of that same limb. A TFNE may resolve partially or completely before recurring again later on during the day.

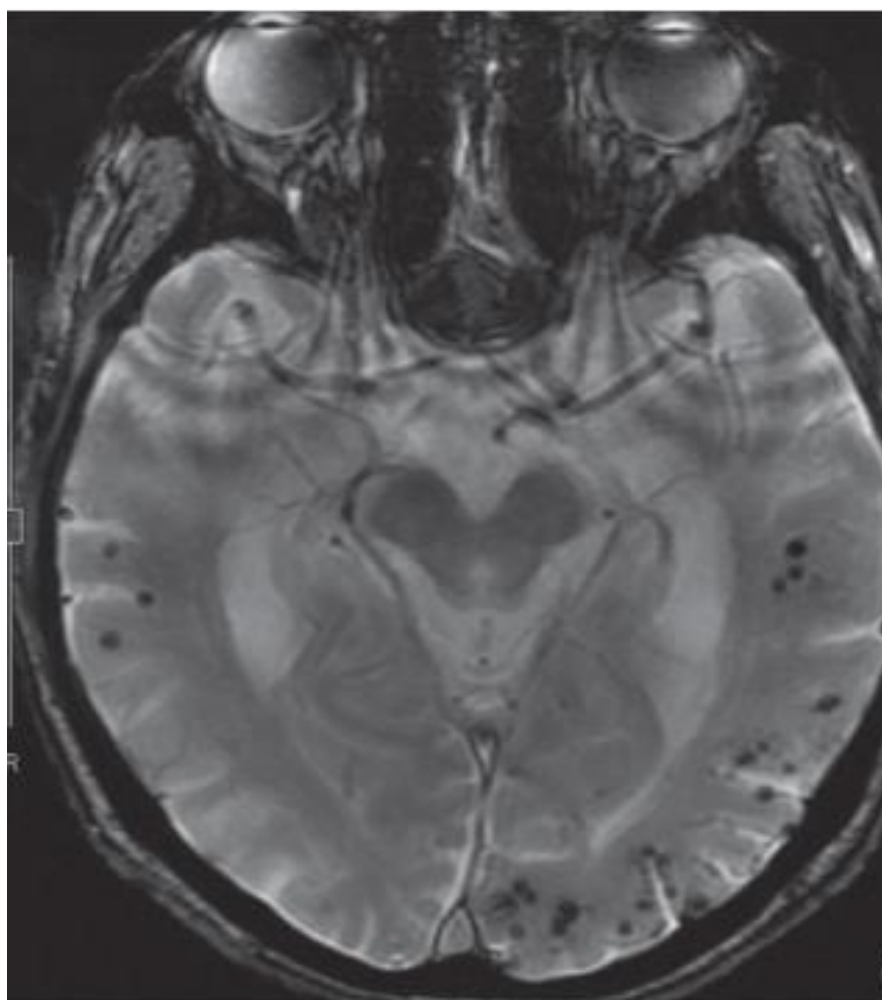
TFNEs with Cerebral Microhemorrhage.

Cerebral microhemorrhage that occur as part of CAA (Figure 1) may be a cause of TFNE's.^{10, 18}

Microhemorrhages are visualised in 47.4% of patients with CAA confirmed on pathology.

Risk for eventual conversion to lobar intracerebral hemorrhage (ICH) is significantly increased at the sites of microhemorrhage. The risk for microhemorrhage is higher in local areas of confirmed CAA and is directly proportional to the density of amyloid deposition in blood vessels. Increasing numbers of microhemorrhages in a localised area may be suggestive of a future ICH so this can be used as a predictive tool. While most cerebral microhemorrhages are usually asymptomatic, microhemorrhages were associated with TFNE's in several case studies.^{6,11-14}

*Figure 1: Multiple bilateral microhemorrhages in a lobar distribution*¹²



TFNEs with Focal Cortical Subarachnoid Hemorrhage and Cortical Superficial Siderosis.

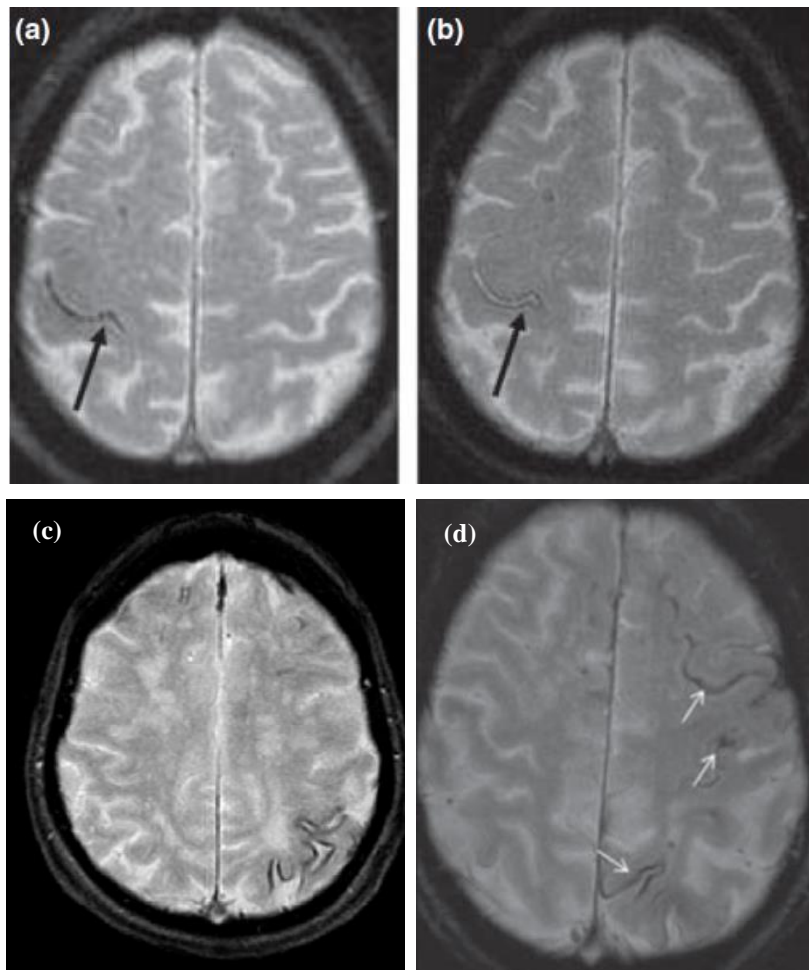
The most frequent cause for TFNE's in CAA is focal cortical subarachnoid hemorrhage with resulting Cortical Superficial Siderosis (CSS).¹⁶ (Figure 2) In CAA, subarachnoid hemorrhages typically occur in a focal convexity pattern along brain areas with a high CAA density.⁴ Eventual conversion to superficial siderosis occurs after blood products are cleared from CSF spaces.⁵ CSS can be defined as hemosiderin deposits in the subpial space that occur after repeated bleeding into the subarachnoid space. CAA-mediated subarachnoid hemorrhage may present with TIA-like symptoms as well as headache and ictal symptoms.⁸⁻⁹

CSS occurs in up to 61% of pathologically confirmed cases of CAA and increases the risk for lobar ICH significantly.^{16,17} Even though CSS

occurs mainly in areas where previous microhemorrhages were present, it generally occurs in patients with CAA with a lower microhemorrhage overall burden.⁴ CSS associated with CAA may also be found in Alzheimer's Dementia and/or mild cognitive impairment patients who have a higher prevalence of CSS when compared to the general population. Current Boston Criteria for diagnosis of CAA does not include subarachnoid hemorrhage.¹⁸⁻¹⁹

15 % of patients with CAA experienced TFNE's at some point in one multicenter cohort study. Patients with CAA and evidence of CSS were more likely to experience TFNE's when compared to CAA patients with no evidence of subarachnoid hemorrhage or CSS (50% vs 19%). 50 % of TFNE patients experienced subsequent ICH over a median period of 14 months.^{1,2}

Figure 2: a) Right rolandic sulcus subarachnoid hemorrhage on T2-Gradient Echo MRI b) Conversion of blood to CSS 8 months later⁸ c) Cortical Superficial Siderosis (CSS) left parietal lobe on T2- Gradient echo in a patient presenting with a transient aphasia and right motor deficit.¹ Also shows bilateral white matter T2 hyperintensity due to leukoencephalopathy. d) CSS in multiple gyri (arrows) in a patient with recurrent spreading parasthesia in right upper limb.¹⁵



TFNEs Associated with Intracerebral Hemorrhage.

ICH is known complication of CAA.(Figure 3) The Helsinki ICH study found that 20% of ICHs occurred in patients with CAA in cortical areas that had higher amyloid angiopathy volume.²²

ICH in CAA patients typically follows a lobar distribution rather than affecting deep structures of the brain as amyloid is deposited preferentially in meningeal and cortical blood vessels. Even though a significant proportion of ICH symptoms never resolve, CAA-mediated ICH has been implicated as a cause for TFNE's with complete resolution of symptoms in these instances.²¹⁻²⁴

TFNEs with Cerebral amyloid angiopathy-related inflammation

Apart from hemorrhagic events, CAA is also associated with transient focal white matter vasogenic edema.(Figure 4) These white matter changes exert a variable degree of mass effect but are not enhanced by contrast. These lesions tend to present with worsening cognition, headache and stroke like symptoms. They may give symptoms spreading gradually to contiguous body parts. These lesions usually present with subacute cognitive changes, seizures and headache. Symptoms are usually transient in nature but they tend to last longer than TFNE's. These lesions may respond to steroids, or immunotherapy.

Figure 3: Intracerebral hemorrhage in a patient with CAA confirmed using Boston criteria. (two separate axial planes from same image)¹⁸

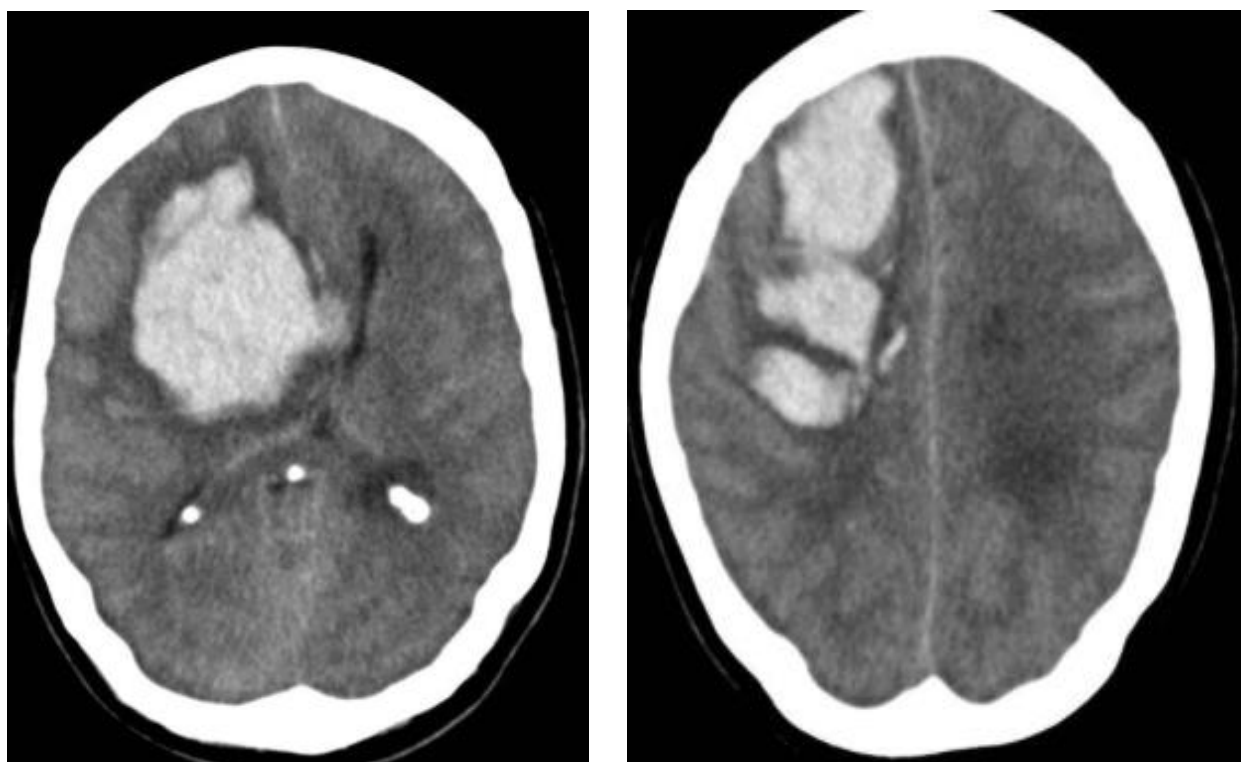
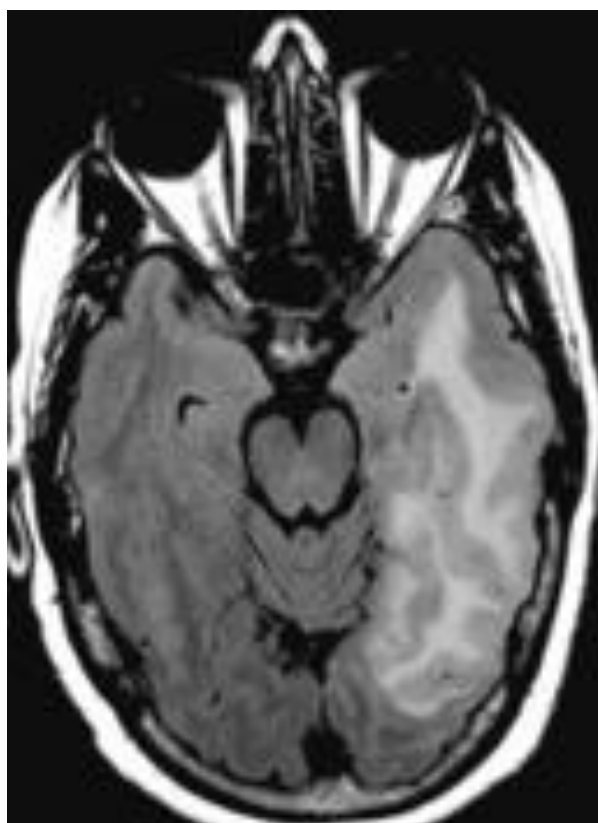


Figure 4: Cerebral amyloid angiopathy-related inflammation involving left temporal and occipital lobes.²⁶



TFNEs with leukoencephalopathy

Leukoencephalopathy (Figure 2c) volume is directly related to CAA volume and tends to occur predominately in the frontal and parietal lobes first (70 % of all patients) followed by temporal and occipital regions (15% and 10 %).^{25,26} Leukoencephalopathy is associated with an increased risk of subsequent ICH in the areas most heavily affected. This finding suggests that ICH in CAA may occur as a result of two separate but related complications of CAA (dysregulated blood flow and increased susceptibility of hemorrhage from blood vessels with amyloid deposits).^{25,26}

Several TIA-like episodes in known CAA patients had no evidence of overt pathology on imaging (subarachnoid hemorrhage, CSS or ICH) but did have a variable degree of leukoencephalopathy. This finding suggests that focal ischemia related to these white matter changes are another cause for TFNE's in CAA.^{7,25,26}

Conclusion

CAA mediated TFNE's are an under-recognized cause of acute neurological symptoms. It is important to keep TFNEs as part of the differential diagnosis when a patient presents with a

presumed TIA. The features distinguishing TIA's from TFNE's should always be sought using appropriate history taking, clinical examination and specific imaging.

Thrombolysis using IV-tPA or oral anticoagulation has been reported in patients with CAA-related TFNE's due to the misdiagnosis with TIA.^{5, 20} Patients with TFNE's treated with thrombolytic therapy or anticoagulation were more likely to develop ICH when compared to those who did not receive therapy.⁶ This finding questions the safety of the usage of anticoagulation / thrombolytic therapy in patients with TIA-like symptoms without prior exclusion of CAA-mediated subarachnoid hemorrhage using specific blood sensitive imaging such as T2-gradient echo MRI.^{5,6,20}

Recent case reports suggest that agents used in migraine prophylaxis (verapamil or topiramate) may have a role in treating frequent recurrent TFNE's that persist over weeks or months and do not resolve spontaneously. In TFNE's caused by cerebral amyloid angiopathy-related inflammation, the lesions may respond to steroids.

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