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Editorial

Cerebral amyloid angiopathy-related transient focal neurological episodes (CAA-TFNEs): A well-defined clinical-radiological syndrome

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Cerebral amyloid angiopathy (CAA), is a common degenerative small vessel disease of the ageing brain resulting from progressive amyloid deposition, predominantly in small arteries and arterioles of the cortex and leptomeninges [1]. CAA is more relevant than ever, since it can now be readily diagnosed during life using validated neuroimaging criteria (aka the Boston criteria) [2,3], particularly with the widespread use of blood-sensitive T2* MRI sequences. Consequently, the dominant theme of CAA-related clinical research and practice in the last decade or so has been the growing appreciation of the diverse manifestations of the disease [4,5]. The sentinel clinical syndrome originally recognized to be directly associated with CAA is spontaneous lobar intracerebral haemorrhage. More recent research has clarified that presentations without major lobar intracerebral haemorrhage are also common in the setting of CAA, and include cognitive impairment and dementia, acute convexity subarachnoid haemorrhage and transient neurological symptoms [6].

Transient focal neurological episodes (TFNEs) caused by CAA (CAA-related TFNEs) are interesting from a pathophysiological perspective, but are in fact one of the most challenging manifestations to diagnose clinically [7]. They consist of short-lived (10 to 30 min, but usually < 5 min), often recurrent stereotyped episodes of focal disturbances (typically somatosensory or motor, though visual or language functions can also be involved), typically exhibiting a spreading onset, where the symptoms smoothly migrate over a few minutes from one body part to another (e.g. from the hand, up the arm into the face, i.e., a cheiro-oral pattern) [7,8], which can occur in patients with CAA [7]. The triggers for CAA-related TFNEs in a substantial proportion of patients presenting with this syndrome appear to be superficial cortical hemorrhages. These superficial cortical bleeds follow the curvilinear shape of the surrounding cerebral gyri - designated as convexity subarachnoid haemorrhage when acute and cortical superficial siderosis (cSS) when chronic - and are now accepted as specific haemorrhagic imaging signatures of advanced CAA [9]. Indeed, in patients with CAA-related TFNEs there is congruence between convexity subarachnoid haemorrhage or cSS topography and the somatotopy of marching neurological deficits, i.e. most often central sulcal convexity subarachnoid haemorrhage or cSS [10] and contralateral somatosensory migrating symptoms. Of note, current evidence suggests that most non-traumatic acute convexity subarachnoid haemorrhage in the elderly and the majority of cortical superficial siderosis may be attributed to CAA [9] - if they happened to occur in eloquent areas they can potentially give rise to CAA-related TFNEs and thus come to clinical attention [10]. The close proximity of these CAA-related superficial cortical or subarachnoid bleeds to the cortical surface is hypothesised to spark an electrophysiological process in cortical neurons and glia, implicating the phenomenon of cortical spreading depolarization, also known as cortical spreading depression. The phenomenological similarities between cortical spreading depolarization pathophysiology and the most conspicuous features of CAA-related TFNEs are quite revealing. For example, the slow spreading pattern, the combination of positive (e.g. tingling) followed by negative (e.g. numbness) symptomatology within a single episode, the stereotypic nature of the spells and complete reversibility (with some similarities shared with migraine aura) strongly support cortical spreading depolarization as the ultimate biologically plausible mechanism.

The difficulty in clinical diagnosis is that similar transient neurological symptoms may occur in patients with other conditions primarily transient ischemic attacks (TIA), focal seizures or migraines with aura. There is only a single prospective study on the proportion of suspected TIA that may instead be CAA-related TFNE. In this study, patients with possible ischemic symptoms consecutively had an MRI: 4/416 (1%) were retrospectively classified as having CAA-related TFNE [11]. The differentiation of CAA-related TFNEs from other neurological syndromes, and TIAs in particular, is imperative given that they herald a high rate of future symptomatic haemorrhage, both lobar intracerebral haemorrhage and acute convexity subarachnoid haemorrhage [7]. This is of major clinical relevance – misclassification of CAA-related TFNEs as TIAs will lead to potentially dangerous use of antithrombotic drugs.

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In a European multicentre study, 50% of patients with CAA-related TFNE had symptomatic lobar ICH (n = 12/24) over a median period of 14 months [8], a rate significantly higher than that observed for recurrent lobar ICH (around 10–15% per year) in unselected patients cohorts presenting with CAA-related ICH. In a meta-analysis of nine small 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%) [12]. This extremely high ICH risk is unlikely to be a direct consequence of TFNEs per se; instead it seems to be mirroring the strong association of TFNE with cortical superficial siderosis, which is the single most important MRI markers of severe leptomeningeal CAA and future bleeding across the whole spectrum of CAA presentations [7,9,13].

Despite an increased clinical awareness and more specific neuroimaging markers which now allow clinicians to diagnose CAA-related TFNEs, the literature on the topic remains somewhat limited, with the majority of clinical studies coming from highly selected CAA research groups. Hence, the report by Montero et al. in this issue of the Journal of the Neurological Sciences is timely to remind us again about CAA-related TFNEs. The authors describe a well-characterised case series of 11 patients admitted to a stroke unit (2014–2018) with recurrent transient focal neurological symptoms and radiological features suggestive of CAA (mean age was 76, range, 66–89 years). All had transient, stereotyped, and recurrent episodes (6 patients had > 10 episodes). Gradual spread of the symptoms was recorded in 9 patients, in whom transient paresthesia with or without numbness, was the predominant phenomenology. In all cases, sensory symptoms affected the perioral region and upper limbs. Based on clinical experience this cheiro-oral presentation might be especially helpful in the differential diagnosis of CAA-related TFNEs vs. TIA or other neurological causes. Three patients were initially misdiagnosed as having recurrent TIAs, 6 as having seizures, and 2 as having both. Two patients were in fact prescribed antiplatelet therapy on a presumed diagnosis of TIAs. Brain MRI with T2* gradient-recalled echo sequences revealed disseminated cortical superficial siderosis in 5 patients, lobar microbleeds in 1 patient, and both features in 5 of the patients. After a median follow-up of 36 months (interquartile range 12–48 months), intracranial haemorrhage was recorded in 4 patients. All 4 had cortical superficial siderosis in the previous brain MRI, and 1 was on antiplatelet therapy. The median delay from the onset of the first TFNEs to the final diagnosis as CAA-related TFNE was 9 months (interquartile range: 1–24 months). In 3 of the 4 patients who developed spontaneous lobar intracerebral haemorrhage, the diagnosis of CAA (and hence the assignment of these episodes as CAA-related TFNE) was only suspected and confirmed after the symptomatic hemorrhagic stroke has happened. Of note, none of the patients in the case series had an alternative explanation other than CAA (no structural brain lesion, atrial fibrillation, extracranial or intracranial stenosis) based on extracranial and intracranial ultrasound examination or CT angiography, transthoracic echocardiogram, and 24 h ECG telemetry. Also none of the patient had a previous history of spontaneous lobar intracerebral haemorrhage raising suspicion for CAA before the occurrence of TFNEs. This is of major relevance since much of original literature on CAA-related TFNEs/acute convexity subarachnoid haemorrhage was based on retrospective diagnosis in patients with CAA-related ICH, or included patient who already had a history of lobar intracerebral haemorrhage.

The paper by Montero et al. has several limitations, including the small sample size and retrospective design. It would have been interesting to know more details regarding where the patients came from - TIA clinics, neurosurgery referrals for acute convexity subarachnoid heaemorrhage on CT, acute stroke unit etc. The proportion of patients with suspected TIA at the authors' center who were likely to have CAA-TFNE is not described. Also, the current cohort is rather confirmatory of previous findings. However, the authors have very diligently characterised the clinical phenomenology (larger systematic studies on CAA-related TFNEs characterization remain limited), MRI features and outcome in this single centre cohort. Despite the limitations in the retrospective design, this very approach is pragmatic for the clinical realm and allows to appreciate that often CAA-related TFNEs are misdiagnosed. Overall, the paper would be of importance in the current literature around CAA-related TFNEs, since it will allow clinicians to appreciate all the clinically relevant points around this syndrome. Some of the most pertinent practical points relevant for patient care are summarised below:

(a) Typical of CAA-related TFNEs is the spreading nature of symptoms in many cases (e.g. the smooth spread of paresthesias, and progression from one body part to another or the build-up and migration of visual disturbances), the frequent stereotyped recurrence and the brief (< 30 min, usually less than a few minutes) duration [7]. While some episodes could have clinical symptomatology similar to “classic” TIAs, many TFNEs, especially with multiple, repeated, stereotyped and brief attacks of positive symptoms do not fit with a clear neurological diagnosis (e.g. partial seizures, TIA or migraine aura) and might be considered “atypical TIAs” or “TIA-mimics” by neurologists [7,14].
(b) CAA-related TFNEs are often (but not always) seen in association with acute or chronic haemorrhagic manifestations of CAA (acute convexity subarachnoid haemorrhage or cortical superficial siderosis) in a corresponding cortical region (usually the central sulcus contralateral to the affected limbs).
(c) A high index of suspicion is needed in making a diagnosis of CAA-related TFNEs. Hence, MRI with SWI/T2* gradient-recalled echo should be considered in all older (age > 55) patients with new symptoms suggesting TFNEs (particularly if the symptoms are recurrent and no other plausible competitive aetiology is present, e.g. carotid stenosis). Blood-sensitive MRI is the only way to allow events to be classified according to the likelihood that CAA may be present and could have caused the event. Given the high specificity of cortical superficial siderosis, a presumed diagnosis of CAA-related could be made if the patient does not typically meet the Boston criteria otherwise.
(d) The consequence of not recognizing CAA-related TFNEs might be important. In contrast to patients with TIA in whom the risk of subsequent ischemic stroke can be reduced by prescribing antithrombotics, the patients with CAA-related TFNE are at very high risk of subsequent lobar ICH[8] that would be exacerbated by antithrombotics. Thus, the clinician that suspects and properly recognizes CAA as the cause of transient symptoms could avoid harm by not prescribing antithrombotics and taking appropriate measures to mitigate future ICH risk.
(e) Related to the previous point, I suggest that symptomatic CAA patients presenting with TFNEs but without lobar intracerebral haemorrhage history should be considered and managed as equivalent to CAA-related intracerebral haemorrhage patients when disseminated cortical superficial siderosis is present on MRI.
(f) For symptomatic relief of CAA-related TFNEs, especially if multiple and troublesome for the patient, a trial of antiepileptic medications (e.g. lamotrigine, levetiracetam) would be reasonable.

Finally, a word on terminology – the less specific term “amyloid spells” has been historically used in the literature to describe these episodes. This term is rather confusing and should be avoided, as it denotes that these symptoms are directly caused by amyloid itself. Instead, the descriptive term CAA-related TFNEs is more accurate in distinguishing the transient neurology symptoms seen in CAA from other causes of temporary neurological disturbances and is now widely adopted in the CAA field. It also reflects their emergence as a better defined and specific clinical-radiological entity associated with CAA. There is a growing need for clinicians to be aware of the diverse clinical manifestations of CAA, including CAA-related TFNEs and for additional research on phenotypes, prognosis, and treatment [6].

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