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Editorial

Elderly and forgetful with transient neurological spells: A story of two amyloids?

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Cerebrovascular amyloid-β deposition within small vessels (i.e. sporadic cerebral amyloid angiopathy—CAA) is perhaps one of the most common neuropathological traits in the aging brain [1,2]. In population-based autopsy studies it is found in 20–40% of non-demented and 50–60% of demented older individuals [3]. CAA also seems to form an integral part in Alzheimer's disease (AD), being present in nearly all brains with AD-type pathology [4] and probably suggesting a close molecular relationship between vascular and parenchymal amyloid-β deposits. Despite this overlap between the two diseases, CAA remains a clinically distinct entity from AD: fewer than half of those individuals who die from CAA actually meet pathologic criteria for AD [1,5] and the majority of AD patients have only mild CAA [6]. In addition to possibly contributing to age-related cognitive impairment and dementia [7,8], CAA is traditionally considered an important risk factor for spontaneous lobar intracerebral haemorrhage and anticoagulant-related bleeding [1,2]. In the era on neuroimaging, CAA is associated with a high prevalence of MRI markers of haemorrhagic and ischaemic brain injury, including multiple strictly lobar microbleeds, cortical superficial siderosis, cerebral microinfarcts and white matter hyperintensities (leukoaraiosis) [1,2].

The interesting case by Safouris and colleagues in this issue of the Journal, reminds us the substantial clinical relevance of CAA during life as well as the expanding clinical-neuroimaging spectrum of the disease. In summary, they describe an elderly patient with probable AD and lobar microbleeds (qualifying for the designation of probable CAA [9,10], Table 1) who developed TIA-like episodes (previously treated with aspirin). After a detailed workup, no evidence of an ischaemic/thromboembolic (or other) mechanism was identified, but instead a new lobar microbleed was detected compared to baseline blood-sensitive MRI scans. In light of these results, the authors' ensuing approach rationally followed the philosophy of Occam's razor, assuming that one dominant mechanism was probably linking AD cognitive decline, lobar microbleeds and TIA-like episodes: brain amyloid—or actually two amyloids, cerebrovascular, co-exiting with parenchymal amyloid-β. After all, transient focal neurological episodes, sometimes called 'amyloid spells', are not uncommon in CAA patients [11]. Although amyloid spells most likely have a heterogeneous pathogenesis (varying from narrowing of amyloid-laden small vessels to seizure-like mechanisms related to microbleeding or attributed to focal convexity subarachnoid haemorrhages) they may be a useful clinical marker of CAA. A recent neuropathological study identified TIA-like episodes as being significant clinical predictors of severe CAA in patients with pathologically confirmed AD [12]. In this study, the prevalence of TIA-like events in participants with both AD and advanced CAA on pathology was striking similar to the reported prevalence in a multicentre MRI-based CAA cohort, at 12.5% [12,13].

The report by Safouris et al. brings to mind an influential article published by Okazaki and colleagues in 1979 [14], which defined the relationship between CAA and lobar intracerebral haemorrhage in 23 consecutive autopsies cases from the Mayo Clinic:

> *'Despite the frequency of cerebral amyloid angiopathy as a pathologic finding and a voluminous pathologic literature concerning its prevalence, morphology, and pathogenesis, the relative infrequency with which clinical symptoms have been ascribed to this disorder is underscored by the fact that it was never suspected on clinical grounds in our patients. It is of interest to note that 3 of our patients had been receiving anticoagulant therapy for what were thought to be transient ischemic attacks at the time of the fatal cerebral hemorrhage.'*[14]

Indeed, although randomised evidence is limited, reasonable steps for limiting the risk of CAA-related haemorrhage are blood pressure control, avoidance of anticoagulation, and as in the current clinical scenario withholding of other antithrombotics in the absence of a clear-cut indication. A recent study compared the risk of future symptomatic intracerebral haemorrhage in patients who presented with strictly lobar microbleeds without a history of intracerebral haemorrhage (cerebral microbleeds-only CAA) vs. patients who presented with CAA-related lobar intracerebral haemorrhage [15]. As in the current case, patients presenting with just lobar cerebral microbleeds on MRI had a clinical, genetic, and neuroimaging profile suggestive of severe underlying CAA pathology. In survival analysis the cerebral microbleeds-only group had a considerable risk of incident intracerebral haemorrhage, although lower compared to the lobar intracerebral haemorrhage cohort. The use of warfarin in a small subgroup of cerebral microbleeds-only CAA patients was associated with a significantly increased risk of future intracerebral haemorrhage after adjusting for

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Table 1
Classic and *modified* Boston criteria for diagnosis of cerebral amyloid angiopathy (CAA). (*Modifications compared to the classic Boston criteria based on Linn et al. [9]).

1. Definite CAA
Full post-mortem examination demonstrating:
- Lobar, cortical, or cortical-subcortical haemorrhage.
- Severe CAA with vasculopathy.
- Absence of other diagnostic lesion.

2. Probable CAA with supporting pathology
Clinical data and pathologic tissue (evacuated haematoma or cortical biopsy) demonstrating:
- Lobar, cortical, or cortical-subcortical haemorrhage.
- Some degree of CAA in specimen.
- Absence of other diagnostic lesion.

3. Probable CAA
Clinical data and MRI or CT demonstrating:
- Multiple haemorrhages restricted to lobar, cortical, or cortical-subcortical regions (cerebellar haemorrhage allowed).
  * [OR single lobar, cortical, or cortical-subcortical haemorrhage and focal[b] or disseminated[c] superficial siderosis].
- Age ≥ 55 years.
- Absence of other cause of haemorrhage[a].

4. Possible CAA
Clinical data and MRI or CT demonstrating:
- Single lobar, cortical, or cortical-subcortical haemorrhage.
  * [OR focal[b] or disseminated[c] superficial siderosis].
- Age ≥55 years.
- Absence of other cause of haemorrhage[a].

[a] Other causes of haemorrhage (differential diagnosis of lobar haemorrhages):
- Antecedent head trauma.
- Haemorrhagic transformation of an ischemic stroke.
- Arteriovenous malformation.
- Haemorrhagic tumour.
- Warfarin therapy with international normalisation ratio > 3.
- Vasculitis.

[b]Focal siderosis: siderosis restricted to 3 or fewer sulci.
[c]Disseminated siderosis: siderosis affecting at least 4 sulci.

other confounders [15]. Nevertheless, aspirin might still be beneficial in some CAA patients when a strong indication is present and the clinicians should carefully weigh the risk–benefits in each case.

Safouris and colleagues provide a timely case report, with a number of clinically relevant take-home messages, potentially useful for neurologists working in a range of different setting, since amyloid spells can resemble not only TIAs, but also migraine auras or seizures (although they are often not quite typical of any of them) [16]. At the very least, the case highlights the key importance of MRI, including appropriate blood-sensitive sequences in the investigation of older demented patients with otherwise unexplained transient neurological spells, the careful balance of future bleeding risk [16] and that CAA might not always be AD's 'silent partner'.

Conflicts of interest

None declared.

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