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In-vivo diagnosis of cerebral amyloid angiopathy: an updated review

Nicolas Raposo^{a,b,c}, Charlotte Périole^{a,b} and Mélanie Planton^{a,c}

Purpose of review

Sporadic cerebral amyloid angiopathy (CAA) is a highly prevalent small vessel disease in ageing population with potential severe complications including lobar intracerebral hemorrhage (ICH), cognitive impairment, and dementia. Although diagnosis of CAA was made only with postmortem neuropathological examination a few decades ago, diagnosing CAA without pathological proof is now allowed in living patients. This review focuses on recently identified biomarkers of CAA and current diagnostic criteria.

Recent findings

Over the past few years, clinicians and researchers have shown increased interest for CAA, and important advances have been made. Thanks to recent insights into mechanisms involved in CAA and advances in structural and functional neuroimaging, PET amyloid tracers, cerebrospinal fluid and plasma biomarkers analysis, a growing number of biomarkers of CAA have been identified. Imaging-based diagnostic criteria including emerging biomarkers have been recently developed or updated, enabling accurate and earlier diagnosis of CAA in living patients.

Summary

Recent advances in neuroimaging allow diagnosing CAA in the absence of pathological examination. Current imaging-based criteria have high diagnostic performance in patients presenting with ICH, but is more limited in other clinical context such as cognitively impaired patients or asymptomatic individuals. Further research is still needed to improve diagnostic accuracy.

Keywords

biomarkers, cerebral amyloid angiopathy, diagnosis

INTRODUCTION

Sporadic cerebral amyloid angiopathy (CAA) is a common small vessel disease (SVD) characterized by the accumulation of amyloid- β ($A\beta$) peptide in the wall of cortical and leptomeningeal vessels [1]. Advancing age is the main risk factor for developing CAA. CAA pathology is found in 20–40% in general aging population and up to 50–60% in demented patients [2]. CAA is a well known cause of lobar intracerebral hemorrhage (ICH), but its clinical spectrum has been recently shown to be much larger, including transient focal neurological episodes (TFNE), rapidly progressive cognitive and neurological decline related to inflammatory CAA, cognitive impairment and dementia [3].

There is currently no known effective therapy for CAA. Nonetheless, treatments targeting $A\beta$ production or clearance are currently in development and clinical trial assessing anticoagulant strategy in these patients are ongoing, raising the perspective of future treatments. Accurate and early diagnosis

of CAA has therefore important prognostic and potential therapeutic implications.

Although diagnosis of CAA was made only with postmortem neuropathological examination a few decades ago, diagnosing CAA without pathological proof is now allowed in living patients, thanks to imaging-based criteria, which have been recently developed or updated [4[■],5].

In this review, we provide a comprehensive update on the latest identified biomarkers and current diagnostic criteria of CAA.

^aDepartment of neurology, Toulouse University Hospital, ^bClinical Investigation Center, CIC1436, Toulouse University Hospital, F-CRIN/StrokeLink Network, Toulouse and ^cToulouse NeuroImaging Center, University of Toulouse, Inserm, UPS, France

Correspondence to Nicolas Raposo, MD, PhD, Service de Neurologie, Hôpital Pierre-Paul Riquet, Centre Hospitalier Universitaire de Toulouse, Place Baylac, 31059 Toulouse Cedex 9, France. Tel: +33 5 61 77 76 40; e-mail: raposo.n@chu-toulouse.fr

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KEY POINTS

- Over the last decades, a growing number of biomarkers of cerebral amyloid angiopathy (CAA) have been identified including hemorrhagic and nonhemorrhagic MRI markers, amyloid PET, ApoE genotype, and circulating biomarkers in plasma and cerebrospinal fluid.
- Neuroimaging-based criteria have been recently developed and updated, enabling accurate diagnosis of CAA in living patients, in the absence of pathological examination.
- Current criteria have high diagnostic performance in intracerebral hemorrhage (ICH) presentations of CAA, but sensitivity is more limited in non-ICH presentations (i.e. cognitive impairment and dementia, asymptomatic individuals).

BIOMARKERS OF CEREBRAL AMYLOID ANGIOPATHY

Initially, diagnosis of CAA required brain tissue neuropathological examination from brain biopsy or necropsy. In the 1990s, diagnosis of CAA was allowed in living patients with the introduction of the Boston criteria when brain imaging demonstrated single or multiple strictly lobar hemorrhages in people aged 55 years or older [6]. During the last decade, important advances in neuroimaging and increased interest from clinicians and researchers for CAA enabled development of novel biomarkers of CAA.

Lobar cerebral microbleeds

Definition and mechanisms: Cerebral microbleeds (CMBs) are silent brain hemorrhages visible on MRI blood-sensitive sequences, characterized by small foci of hemosiderin deposits [7]. CMBs are well known neuroimaging markers of SVD, and their distribution is suggestive of SVD subtype [8[•]]. While lobar CMBs are associated with CAA, nonlobar CMBs indicate arteriolosclerosis (also named hypertensive angiopathy) [9^{••}].

Detection: CMBs appear as small (2–10 mm), hypointense, ovoid or round lesions on T2*-weighted gradient recalled echo (T2*-GRE) or susceptibility weighted (SWI). See figure for illustrative images. Guidelines for detection and mimics have been published [10,11^{••}].

Link with CAA: Lobar CMBs are neuroimaging markers of CAA included in the MRI-based Boston criteria [4^{••}]. Importantly, the clinical context (ICH, cognitive impairment, ischemic stroke, healthy population) and other imaging markers of SVD

may affect the diagnostic and prognostic (e.g. risk of ICH or cognitive decline) value of CMBs, and should be therefore considered when evaluating CMBs.

Cortical superficial siderosis

Definition and mechanisms: Cortical superficial siderosis (cSS) refers to linear deposits of hemosiderin on the surface of the CNS, restricted to the convexity of the brain hemisphere [12]. Increased evidence suggest that cSS may result from repeated bleeding within the subarachnoid spaces [13–16].

Detection: cSS is defined as a homogeneous hypointense curvilinear signal intensity on T2*-GRE or SWI in the cerebral cortex, within the subarachnoid space, or both [17]. cSS is typically delineated on blood-sensitive sequences as two almost parallel, bilinear hypointensities within the cortex, showing a “tracklike” appearance [18].

Link with CAA: Growing evidence suggests that cSS is a key neuroimaging marker of CAA. Although cSS is detected in 0.7% of the general population [19], prevalence of cSS is 20% in patients with CAA without ICH [20] and 40–60% in CAA patients with ICH [20–22]. In a validation MRI-pathology study, cSS was observed in 23 of 38 patients with pathologically-proven CAA vs. 0 of 22 subjects with ICH not related to CAA [22]. cSS has been linked to transient focal neurological episode [23] and APOE ε2 allele [24], and is included in the MRI-based Boston criteria [4^{••},22].

Convexity subarachnoid hemorrhage

Definition and mechanisms: In patients with CAA, acute convexity subarachnoid hemorrhage (cSAH) can occur in two distinct contexts: (a) in the absence of acute ICH (isolated cSAH), or (b) simultaneously with acute lobar ICH. Two main mechanisms have been advanced to explain cSAH in CAA: (i) leakage from a lobar ICH into the subarachnoid space; (ii) rupture of meningeal vessels directly into the subarachnoid space [17].

Detection: Isolated cSAH corresponds to a subarachnoid bleeding confined to the convexities of the brain that does not extend into the parenchyma, sylvian fissures, ventricles, or basal cisterns [25]. In general, both noncontrast CT and MRI can detect acute subarachnoid hemorrhage with high sensitivity [26–29]. On MRI, acute cSAH appears as linear hyperintense signal on FLAIR (suggestive of acute blood), with a corresponding hypointense signal (but not constant) on T2*-GRE or SWI in the subarachnoid space that affected one or more cortical sulci of the cerebral convexities. In patients with

CAA, acute cSAH is more frequently observed in association with an acute lobar ICH.

Link with CAA: A growing number of cohort studies have linked CAA and isolated cSAH [30–34]. CAA is now considered as the main cause of cSAH in subjects older than 60 years [25,35]. The clinical presentation of cSAH related to CAA consisted typically in TFNEs and cSS is observed in up to 90%. Recent studies of patients with acute ICH suggest that presence of cSAH is independently associated with underlying CAA pathology and is now included in the CT-based Edinburgh criteria [5]. cSAH may also be a risk factor for ICH recurrence in patients with CAA-related ICH [36].

White matter hyperintensities

Definition and mechanisms: CAA is also recognized as a significant contributor to white matter hyperintensities (WMH). Growing evidence suggest that beta-amyloid accumulation in the vessel wall can lead to impaired vascular reactivity, resulting in hypoperfusion [37,38].

Detection: The Boston Criteria v2.0 integrate WMH features as novel MRI marker for CAA with multispot spatial distribution, defined as more than ten T2-weighted FLAIR small circular or ovoid hyperintense lesions in the subcortical white matter of both hemispheres [4**].

Link with CAA: Although WMH multispot pattern is associated with CAA-related ICH and other imaging markers of CAA (i.e. lobar CMBs and enlarged perivascular spaces in the centrum semiovale), a WMH peri-basal ganglia pattern is associated with Hypertension-related ICH and imaging markers of arteriolosclerosis (i.e. deep CMBs and enlarged perivascular spaces in the basal ganglia) [39].

Enlarged perivascular spaces

Definition and mechanisms: Perivascular spaces are extensions of the extracerebral fluid space around small cerebral vessels as they course from the brain surface into and through the brain parenchyma [40,41]. They are usually not visible on conventional neuroimaging. However, they become visible on MRI when enlargement of the potential space occurs, possibly secondary to impaired interstitial fluid drainage and are named enlarged perivascular spaces (EPVS) [42].

Detection: EPVS are defined as small (< 3 mm) round or linear CSF isointense lesions (T2-hyperintense and T1/FLAIR hypointense with respect to brain) along the course of penetrating arteries [43]. They can be detected in the centrum semiovale

(CSO) white matter, the basal ganglia (BG), the hippocampus and the midbrain. Several visual rating scales have been developed and validated [44,45].

Link with CAA: EPVS are emerging markers of SVD, observed both in CAA and hypertension angiopathy (i.e. arteriolosclerosis). Their distribution pattern may suggest the underlying SVD. EPVS in the basal ganglia (BG-EPVS) have been linked to hypertension and imaging markers of hypertensive angiopathy (i.e. lacunes, WMH and deep CMB) whereas EPVS in the CSO (CSO-EPVS) are associated with Alzheimer disease (AD) as well as MRI markers of CAA, amyloid PET positivity and CAA pathology [44,46–54]. Severe CSO-EPVS are now included in the Boston criteria V2.0 [4**].

Apolipoprotein E genotype

Definition and mechanisms: The apolipoprotein E (ApoE) gene, located in chromosome 19q13.2, comprises 3 alleles ($\epsilon 2$, $\epsilon 3$, and $\epsilon 4$). Compared to the most common APOE $\epsilon 3$ homozygous genotype, ApoE $\epsilon 2$ and/or $\epsilon 4$ allele carriers have increased risk of CAA.

Link with CAA: ApoE genotype is the most important genetic risk factor identified for sporadic CAA. Neuropathological studies suggested that APOE $\epsilon 4$ may enhance vascular A β deposition in a dose-dependent fashion, while APOE $\epsilon 2$ promotes vascular breakdown of amyloid-laden vessels [55–57]. Cohort studies reported that APOE $\epsilon 2$ was associated with cSS [58] and increased risk of symptomatic ICH [59] whereas APOE $\epsilon 4$ was linked to higher burden of lobar CMBs [24].

Amyloid positron emission tomography (PET)

Definition and mechanisms: Detecting during life vascular amyloid deposition rather than brain injury may have important implications. Amyloid PET tracers, originally developed to identify amyloid plaques in AD, have been evaluated in CAA.

Detection: Different amyloid PET tracer and methods allow in vivo detection and/or quantification of amyloid deposition in brain parenchyma and vessels. Visual assessment of PET images and quantitative methods are commonly used to analyze amyloid PET.

Link with CAA: Amyloid PET using ^{11}C -PiB and ^{18}F -florbetapir radiotracers has been assessed in cross-sectional studies [60–67]. Most of these studies have shown that amyloid tracer retention was increased in patients with CAA compared to controls [68]. Due to limited sample sizes and heterogeneity across studies with different radiotracer,

PET analysis methods and control groups, the value of amyloid PET for diagnosing CAA remain uncertain. Future large PET studies including subjects with pathological examination for CAA would be of great interest.

Circulating biomarkers

Definition and mechanisms: Detecting amyloid biomarkers – originally developed in AD – in the cerebrospinal fluid (CSF) or in the plasma may help in diagnosing CAA, providing evidence of amyloid pathology.

Detection: Core CSF biomarkers have been explored in CAA patients. However, the number of studies on this topic is limited and the sample sizes of CAA cohorts are small ($n < 20$). Plasma biomarkers may offer several potential advantages compared to CSF biomarkers (less invasive) or amyloid PET (less expensive). Nonetheless, amyloid biomarkers have low concentrations in blood, constituting an important technical challenge.

Link with CAA: Compared to healthy controls, patients with AD show decreased level of A β 42 (without decreased level of A β 40) with increased level of total tau (t-tau) and phosphorylated tau (p-tau) in CSF. A meta-analysis of CSF biomarkers in sporadic CAA have shown that patients with CAA had decreased level of both A β 40 and A β 42 with mild increase in t-tau and p-tau levels [69]. This specific pattern of A β 40/A β 42 is consistent with pathological observations that showed predominantly A β 42 in amyloid plaque although vascular amyloid contains substantial amounts of A β 40 in addition to A β 42 [70]. To date, evidence of a potential role of plasma amyloid biomarkers in CAA are scarce with conflicting data [71,72]. Nonetheless, high-performance plasma amyloid- β biomarkers have been recently developed in AD, showing high performance in predicting brain amyloid- β burden [73–77]. Their clinical utility in CAA has not yet been assessed.

Other candidate biomarkers

Advances in neuroimaging enabled development of novel techniques that may be of interest as a diagnostic tool and/or a marker of disease severity. Those include small acute ischemic lesions on diffusion-weighted imaging (DWI) [78–81] or cortical microinfarcts visible on 7 T MRI, but also on 1.5 or 3 T MRI [82,83]. Evaluating brain network connectivity using diffusion tensor imaging (DTI) – a noninvasive MRI method to quantify microscopic white matter tissue injury – may also be useful, as a marker of CAA severity [84–87]. Techniques assessing

cerebrovascular reactivity, which is altered in CAA, might be useful for early diagnosis of CAA. Among them, functional MRI [blood oxygen level-dependent (BOLD) response] may be more sensitive methods to detect cerebrovascular dysfunction in CAA patients, showing altered response to visual stimuli compared to healthy controls [88,89].

DIAGNOSTIC CRITERIA FOR CEREBRAL AMYLOID ANGIOPATHY

Definite diagnosis of CAA requires histopathological evaluation of brain tissue from autopsy or biopsy samples showing characteristic vascular lesions and accumulation of amyloid β peptide in the cerebrovascular wall of cortical and leptomeningeal vessels. During the last decades, important advances in neuroimaging have been made and diagnostic imaging-based criteria have been developed or updated, enabling CAA diagnosis in living patients in the absence of pathological examination.

The Boston criteria

The Boston criteria are the most widely used criteria for CAA diagnosis in research and clinical practice. The original Boston criteria (v 1.0) were first introduced in 1995 and validated in a small ($n = 39$) single center cohort study [6]. They included the following categories: (a) definite CAA, based on pathological proof of CAA on full autopsy, (b) probable CAA (with or without pathological proof), defined as evidence of at least 2 brain hemorrhages strictly located to lobar (i.e. cortical and cortico-subcortical) regions, including ICH and CMBs, (c) possible CAA, defined as a single lobar hemorrhage.

In 2010, the Boston criteria were revised with the introduction of cSS, as an additional diagnostic imaging marker, and validated in a single cohort study ($n = 60$). These revised criteria are known as the modified Boston criteria (v 1.5) [22].

The original Boston criteria have high sensitivity and specificity, and the modified Boston criteria have shown improved sensitivity without lowering specificity compared to the original Boston criteria. However, the validity of these MRI-based Boston criteria suffered from several limitations including the limited sample size (< 100) and the monocentric design of imaging-pathological studies [6,22,51]. In addition, included patients had predominantly ICH clinical presentations, where the Boston criteria may have higher diagnostic performance compared to non-ICH presentations (i.e. cognitive impairment, TFNE).

To address these issues, a large international multicenter MRI-pathological study was designed

across the International CAA Association network. This study, published in 2022, allowed to update and validate the Boston criteria v 2.0 in a large multicenter cohort ($n = 341$). Key changes of these updated criteria include (a) integration of emerging white matter MRI markers of CAA (i.e. severe visible perivascular spaces in the centrum semiovale and white matter hyperintensities in a multispot pattern), (b) patient's age 50 years and older (vs. 55 years and older in the Boston criteria v 1.5), (c) applicable to subjects either with ICH or non-ICH presentations. Compared to the Boston criteria v 1.5, the Boston criteria v2.0 have higher sensitivity (79.8% vs. 70.8%) and comparable specificity (84.7% vs. 88.8%). As observed with criteria v 1.5, sensitivity of the Boston criteria v 2.0 appears to be higher in ICH presentations than non-ICH presentations.

The Edinburg criteria

Since MRI is sometimes contraindicated, not tolerated or unavailable in the setting of acute ICH, the Edinburg CT and genetic diagnostic criteria have been developed to diagnose underlying CAA in

patients with acute lobar ICH, in the absence of brain MRI and pathological examination [5]. Those included the presence of ApoE $\epsilon 4$ allele and 2 characteristic CT feature of CAA-related ICH including finger-like projections and subarachnoid hemorrhage. In a cohort of 62 patients with severe lobar ICH who died and had postmortem pathological evaluation, the Edinburg criteria had a 96% (95% CI, 78–100) rule in specificity when at least 2/3 markers were present (high risk), and a 100% (95% CI, 88–100) rule out sensitivity in the absence of these markers (low risk) [8[]].

CONCLUSION

Over the last decades, a growing number of biomarkers have been identified thanks to recent insights into mechanisms involved in CAA provided by animal models and advances in structural and functional neuroimaging, PET amyloid tracers, circulating biomarkers analysis. Current diagnostic criteria have high sensitivity and specificity in ICH presentations of CAA, but have lower performance in other clinical context such as cognitive

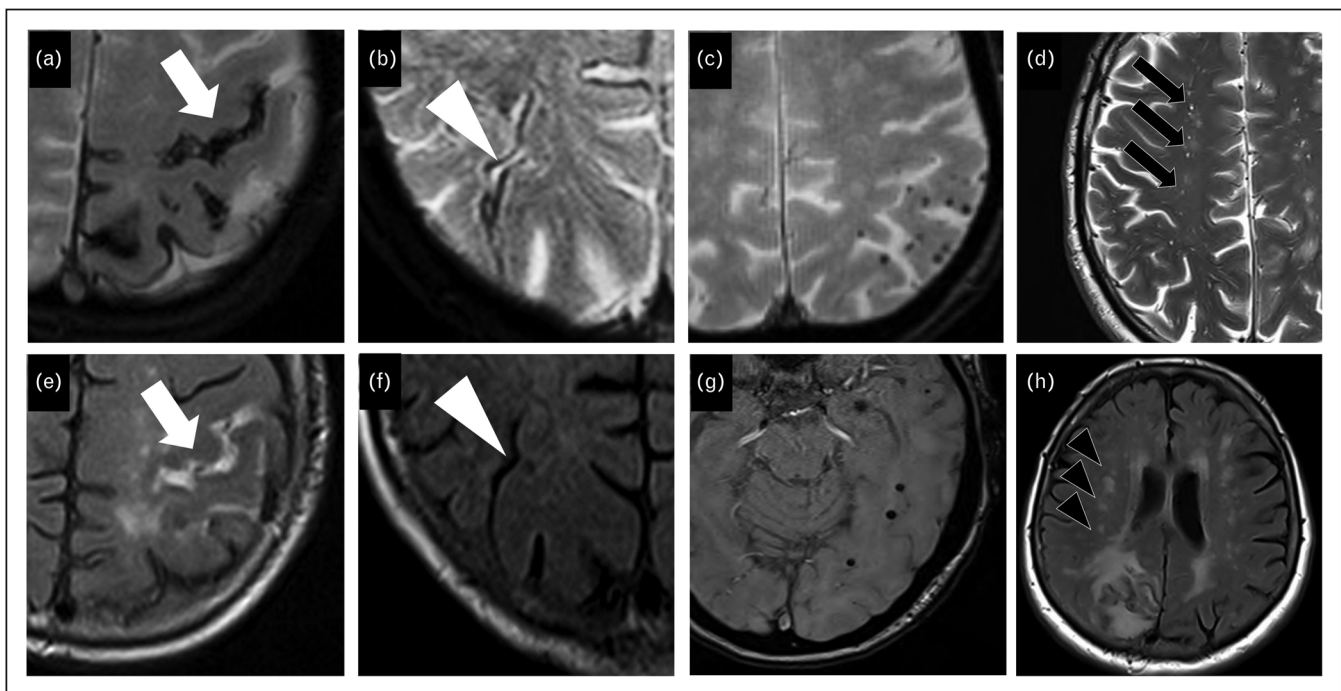


FIGURE 1. MRI markers of cerebral amyloid angiopathy. (a, e) Convexity subarachnoid hemorrhage (white arrow) appearing as linear hypointense signal on T2*GRE (a), with a corresponding hyperintense signal on FLAIR (e) in the subarachnoid space that affected two cortical sulci of the cerebral convexities. (b, f) Cortical superficial siderosis (white arrowhead) delineated on T2*GRE (b) as two almost parallel, bilinear hypointensities within the cortex, showing a tracklike appearance, without corresponding hyperintense signal on FLAIR (f). (c, g) Multiple lobar cerebral microbleeds visible as small round hypointense signal on T2*GRE (c) and SWI (g). (d) Severe enlarged perivascular spaces in the centrum semiovale (black arrows) visible on T2-weighted imaging (i.e., more than 20 visible perivascular spaces in the centrum semiovale of one hemisphere). (e) White matter hyperintensities (black arrowheads) in a multispot pattern (i.e., more than 10 small circular or ovoid T2-weighted FLAIR hyperintense lesions in the bilateral subcortical white matter).

presentation or mixed hemorrhages (i.e. presence of both deep and lobar hemorrhages) [90,91]. Further research is needed to evaluate whether novel biomarkers including amyloid PET and circulating biomarkers would improve diagnostic accuracy (Fig. 1).

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Dr Raposo has received consulting fees from Novartis. The other authors have no conflicts of interest.

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