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Advances in cerebral amyloid angiopathy imaging

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Abstract: Cerebral amyloid angiopathy (CAA) is a cerebral small vessel disease caused by β -amyloid (Aβ) deposition at the leptomeningeal vessel walls. It is a common cause of spontaneous intracerebral hemorrhage and a frequent comorbidity in Alzheimer's disease. The high recurrent hemorrhage rate in CAA makes it very important to recognize this disease to avoid potential harmful medication. Imaging studies play an important role in diagnosis and research of CAA. Conventional computed tomography and magnetic resonance imaging (MRI) methods reveal anatomical alterations, and remains as the most reliable tool in identifying CAA according to modified Boston criteria. The vascular injuries of CAA result in both hemorrhagic and ischemic manifestations and related structural changes on MRI, including cerebral microbleeds, cortical superficial siderosis, white matter hyperintensity, MRI-visible perivascular spaces, and cortical microinfarcts. As imaging techniques advance, not only does the resolution of conventional imaging improve, but novel skills in functional and molecular imaging studies also enable *in vivo* analysis of vessel physiological changes and underlying pathology. These modern tools help in early detection of CAA and may potentially serve as sensitive outcome markers in future clinical trials. In this article, we reviewed past studies of CAA focusing on utilization of various conventional and novel imaging techniques in both research and clinical aspects.

Keywords: cerebral amyloid angiopathy, cerebral microbleed, magnetic resonance imaging, positron emitting tomography, small vessel disease

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Introduction

Cerebral amyloid angiopathy (CAA) is caused by deposition of β-amyloid (Aβ) in the tunica adventitia and tunica media of the small to medium sized vessels at cerebral cortex and overlying leptomeninges.[1] Aging and Alzheimer's disease (AD) are the two most common risk factors for CAA, and the prevalence of CAA is strikingly high in the elderly.[2,3] Several genetic mutations that interfere with amyloid metabolism, such as apolipoprotein E (APOE) polymorphism and mutation in amyloid-β protein precursor (APP) gene, are also known to promote spontaneous CAA or even cause hereditary CAA.[3]

Clinical manifestations of CAA are heterogeneous, and include spontaneous lobar intracerebral macrohemorrhage (ICH), transient focal neurological episodes (TFNEs), CAA-related inflammation and cognitive impairment.[1] Lobar ICH in CAA is a devastating disease for its high recurrence rate (estimated at more than 10% per year), especially in patients who are receiving anti-thrombotic agents.[1] Therefore, it is important to recognize CAA in stroke patients in order to avoid potential harmful medication and to offer appropriate prevention from disease progression.

Currently, the gold standard in diagnosing definite CAA requires histopathology confirmation by postmortem autopsy.[4] In clinical practice, most CAA patients are recognized under assistance of magnetic resonance imaging (MRI)

Table 1. Modified Boston criteria for CAA-related hemorrhage.

	Description
Definite CAA	Full postmortem examination demonstrating: Lobar, cortical, or corticosubcortical hemorrhage Severe CAA with vasculopathy Absence of another diagnostic lesion
Probable CAA with supporting pathology	Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating: Lobar, cortical, or corticosubcortical hemorrhage Some degree of CAA in specimen Absence of another diagnostic lesion
Probable CAA	Clinical data and MRI or CT demonstrating: Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed) or Single lobar, cortical, or corticosubcortical hemorrhage and focal or disseminated* superficial siderosis Age ⩾ 55 years Absence of other cause of hemorrhage or superficial siderosis
Possible CAA	Clinical data and MRI or CT demonstrating: Single lobar, cortical, or corticosubcortical hemorrhage Focal or disseminated* superficial siderosis Age ⩾ 55 years Absence of other cause of hemorrhage or superficial siderosis

*Focal superficial siderosis: siderosis restricted to three or fewer sulci; disseminated superficial siderosis: siderosis affecting at least four sulci.
Adapted from 'Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy' by Linn and colleagues.[4]
CAA, cerebral amyloid angiopathy; CT, computed tomography; MRI, magnetic resonance imaging.

with blood-sensitive sequences. According to modified Boston criteria, patients older than 55 years who develop multiple strictly lobar, cortical or corticosubcortical hemorrhage, including ICH and cerebral microbleeds (CMBs), or single lobar hemorrhage plus focal or disseminated cortical superficial hemosiderosis (cSS), could be diagnosed with probable CAA after excluding other possible causes of hemorrhagic events (Table 1).[4] The MRI-based criteria have been shown very accurate in CAA diagnosis in the radiologic/pathologic validation studies.[4,5]

Studies in CAA have been growing rapidly in recent years. Several review articles have discussed the epidemiology, clinical aspects, and pathophysiology of CAA.[1,3,6] With the fast-moving research and emergence of novel imaging techniques, we summarize the important results of recent studies in conventional structural, functional and molecular imaging tools of CAA, and thoroughly describe their clinical and pathological significances in this review.

CAA as a major etiology of spontaneous lobar ICH

CAA is one of the most common etiology of symptomatic ICH (accounts for 12–20%), especially in older patients.[7–9] ICH associated with CAA is characteristically located at lobar or superficial areas [Figure 1(a)] in contrast with ICH associated with hypertensive vasculopathy which mainly involves deep gray matter and brainstem.[10] It is generally agreed that ICH recurrence rate is substantially greater in CAA compared with ICH related to hypertensive microangiopathy.[3,11] MRI markers, including cSS and convexity subarachnoid hemorrhage (cSAH) predict recurrent ICH in CAA patients.[6,12]

TFNEs, the second most common presentation other than lobar ICH, have been recognized as the earliest sign in CAA.[13,14] TFNEs may mimic transient ischemic attack (TIA), migraine aura or seizure.[13] Typically, TFNEs appear as recurrent, stereotyped, brief episodes of focal negative neurological symptoms (such as paresthesia, weakness, or dysphasia) lasting for less than 30 min.[13]

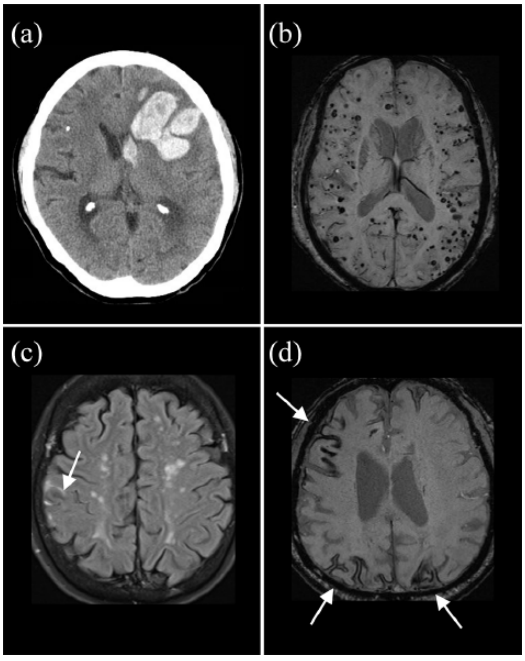

Figure 1. Hemorrhagic presentations in cerebral amyloid angiopathy.
(a) Brain computed tomography shows a left frontal lobar intracerebral hemorrhage with irregular hematoma border and finger-like projection. (b) SWI shows numerous lobar cerebral microbleeds restricted at corticosubcortical areas. (c) T2-FLAIR MRI shows a hyperintense lesion within sulci of cortical surface (arrow), indicating convexity subarachnoid hemorrhage. (d) Cortical superficial siderosis is revealed by SWI as hypointense curvilinear signals along the cortical gyri (arrows).
FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; SWI, susceptibility-weighted imaging.

Some episodes may consist of 'aura-like' visual or sensory symptoms, which typically have a cheiro-oral pattern.[14] TFNEs closely relates to cSS, cSAH and CMBs, and predicts a high risk of early spontaneous ICH.[13,14] In clinical practice, it is important to distinguish TFNEs from other similar neurological deficits, especially TIA, for that the use of anti-thrombotic agents in TIA might actually increase the risk of spontaneous ICH in CAA with TFNEs.[13,14]

In addition to the above acute symptoms, CAA may also present with a subacute course. In CAA-related inflammation, patients develop subacute onset of headache, seizure, cognitive impairment or focal neurological symptoms that respond to immunosuppressive therapy.[15] Imaging studies in these patients typically demonstrate asymmetric, large T2-hyperintense white matter lesion with a corresponding T1-hypointense appearance, and a pattern of vasogenic edema.[15] This imaging presentation is similar to amyloid-related imaging abnormalities that characterized by parenchymal vasogenic edema with sulcal effusions or microhemorrhage, a condition that usually present in patients with AD who receive anti-Aβ monoclonal antibody.[15,16] It is believed that CAA-related inflammation and amyloid-related imaging abnormalities share a similar pathophysiological pathway consisting of an immune response to Aβ deposition in vessel walls.[15]

Finally, CAA can cause progressive cognitive decline and even dementia.[3] Studies have shown that CAA independently contributes to cognitive impairment in spite of having comorbid ICH and AD pathology.[1,17] In contrast with the patients with AD that characteristically manifest as prominent episodic memory impairment, the cognitive decline attributed to CAA has predominant features of slow processing speed, impairment in executive function, attention and to a lesser extent, episodic memory.[18]

Currently, MRI study is essential in diagnosing CAA according to modified Boston criteria.[19] As a result, it is important for clinical physicians to be familiar with the imaging features of CAA so as to give correct diagnosis and early preventive treatment.

Conventional neuroimaging characteristics of CAA

In CAA, the vascular injuries cause both hemorrhagic and ischemic events that can be detected using MRI.[3] Typical hemorrhagic changes seen on imaging studies are lobar ICH, CMBs, cSS, and cSAH, as shown in Figure 1. Other MRI characteristics that can be associated with CAA include white matter hyperintensities (WMHs), MRI-visible perivascular spaces (PVSs), and cortical microinfarcts, as shown in Figure 2.

Cerebral microbleeds

CMBs result from blood extravasation due to microangiopathy (either CAA or hypertensive vasculopathy) and present as small, hypointense lesions that can be demonstrated on gradient echo (GRE) or susceptibility-weighted imaging (SWI) MRI sequences [Figure 1(b)].[20] These lesions typically have a diameter of 2 to 5 mm and

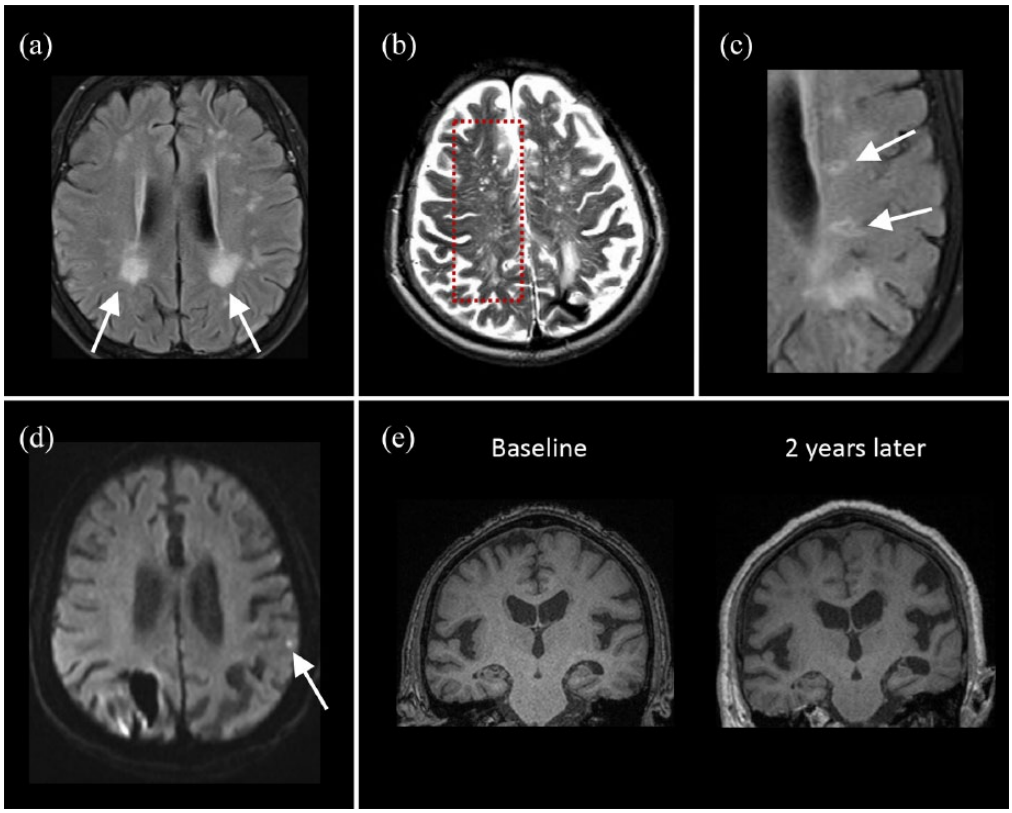

Figure 2. Ischemic presentations in cerebral amyloid angiopathy.
(a) T2-FLAIR MRI shows white matter hyperintensities with posterior predominant pattern (arrows). (b) MRI-visible perivascular spaces located at centrum semiovale are depicted on T2-weighted MRI as hyperintense signals with linear or dot-like appearance. (c) T2-FLAIR MRI shows ovoid lesions with hyperintense rim at periventricular areas, suggestive of lacunar infarcts. (d) High resolution diffusion-weighted imaging study shows a hyperintense dot in the cortical region, indicative of cortical microinfarct. (e) Progressive brain volume loss is shown on longitudinal follow up of T1-MRI studies in 2 years.
FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

are not visible on conventional T1-weighted, T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences.[20,21] The MRI appearance of CMBs should be differentiated from several similar imaging findings, such as flow voids, calcification, iron deposition and cavernous malformation.[21]

The topography of CMB distribution has been considered as an important marker for underlying cerebral small vessel disease (SVD). CMBs strictly located at lobar areas are indicative of CAA while deeply seated CMBs are suggestive of hypertensive vasculopathy. It has been shown that lobar CMBs can be used as a diagnostic marker for CAA in hospital-based populations with the positive predictive value reaching 87.5%.[22] However, the same study also showed that the positive predictive value dropped to 25% in the general population, suggesting that lobar CMBs may be a more accurate CAA marker in patients with related clinical symptoms.[22] On the other hand, the underlying microangiopathy in patients with concomitant presence of lobar and deep CMBs (mixed CMBs) is still controversial, but has been shown harboring hypertensive SVD in recent studies.[23,24]

CMBs in CAA have been attributed to amyloid deposition at vessel walls leading to vessel ruptures.[21,25,26] Using amyloid-positron emission tomography (PET), which will be discussed further in the following section, and conventional MRI measures, studies found a spatial correlation between CMBs and areas of increased amyloid burden, further supporting this concept.[25,26] However, recent histopathological studies with high resolution MRI showed that there may be

less amyloid deposition at areas presenting CMBs, and that vasculopathy and hemorrhagic microinfarct in addition to microhemorrhage were found correlating to CMBs.[27,28] These findings suggested other possible mechanisms linking CAA and CMBs, and more studies are needed to reveal the complicated connection between CAA and CMBs.

The detection of CMBs is associated with important clinical aspects. Studies showed that functional outcome and mortality were worse in ICH patients with positive CMBs.[21,29] Application of anti-thrombotic agents (including intravenous thrombolysis therapy) in patients with high burden of CMBs may increase risk of symptomatic ICH and should be evaluated carefully and individually.[21,30–32] Furthermore, plenty of studies have discussed the relationship between CMBs and cognitive dysfunction.[29,33–37] It has been shown that the presentation of multiple CMBs is a risk factor for cognitive dysfunction in both nondemented elderly and patients with subcortical vascular dementia.[29,33–35] CMBs are also associated with increased risk for progression from mild cognitive impairment to AD as well as worse cognitive function in AD patients.[36,37]

Cortical superficial siderosis

cSS refers to the curvilinear, homogeneous hypointense lesion that follows the gyral cortical surface and can be demonstrated on blood-sensitive MRI sequences [Figure 1(d)].[12] This lesion may have a 'track-like' appearance that results from hemosiderin accumulating at bilateral sides of cortical sulcus in subacute and chronic stages of cSAH [Figure 1(c)].[12] According to the involved areas, cSS could be divided into focal (less than four sulci affected) and disseminated types.[12] cSS should be differentiated from classical superficial siderosis, which predominantly affect infratentorial areas and may result in hearing loss, ataxia or myelopathy.[38]

cSS is now considered as a specific marker of CAA.[19] Studies have shown that cSS presented in 40 to 60% of CAA patients while rarely seen in patients with non-CAA-related ICH and SVD.[12,39] One study, which compared imaging features of SVD between cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and CAA, found that cSS was the only marker that exclusively occurred in CAA while other imaging features were detected in both groups.[39] Adding cSS to the classic Boston criteria increased the sensitivity in detecting CAA by nearly 5% (from 90% to 95%) without affecting the specificity.[19] The extension of cSS involvement may reflect a widespread amyloid-laden cortical and leptomeningeal vessel rupture, and the increasing amounts and multifocality of cSS correlate to the greater risk of ICH in patients with CAA.[12,40]

White matter hyperintensities (leukoaraiosis)

WMHs refer to bilateral, mostly symmetrical, white matter hyperintense lesions demonstrated on T2-weighted imaging study with corresponding iso- or hypointense appearance on T1-weighted sequence [Figure 2(a)].[20] The pathophysiology in WMH is probably associated to chronic ischemic changes, brain tissue damage, blood–brain barrier (BBB) disruption, decreased vascular integrity, and interference with capillary permeability.[41] The distribution pattern of WMH has been shown to reflect different kinds of underlying vascular pathologies.[42] A study revealed that multiple (>10), subcortical lesions were associated with CAA while peri-BG lesions were more often related to hypertensive vasculopathy.[43] Other studies have found that as frontal or equally distributed WMHs were the most common pattern in healthy elderly, posterior predominant WMHs were more frequently seen in CAA.[42,44]

Clinically, WMHs relate to cognitive impairment predominantly in executive function and processing speed, which may be attributed to interruption in nerve fibers connecting different lobes and areas caused by chronic ischemic changes.[45] Increased amounts of WMHs predict higher risk of recurrent lobar ICH in CAA, a larger hematoma size and a greater proportion of hematoma expansion.[41,45]

MRI-visible perivascular spaces

PVSs are extensions of subarachnoid spaces that surround small penetrating cortical arterioles and venules as they run from brain surfaces into brain parenchyma, draining cerebrospinal fluid (CSF) to ventricles.[20,46] Enlarged PVSs that could be seen on MRI study are termed MRI-visible PVSs, which is one of the imaging features of SVD.[47] MRI-visible PVSs are linear or dot-like structures depending to the different imaging angle with the

vessels [Figure 2(b)].[20] The signal intensities are similar to CSF showing hyperintensities on T2-weighted sequences and hypointensities on T1-weighted imaging studies.[20]

CAA and hypertensive vasculopathy are related to MRI-visible PVSs with different distributions.[48] MRI-visible PVSs, mainly at the centrum semiovale (CSO), are associated with CAA-related imaging findings including lobar ICH, CMBs and cSS, suggestive of a connection between MRI-visible PVSs at CSO and CAA.[48] In contrast, MRI-visible PVSs predominantly at the basal ganglion are linked to hypertensive vasculopathy implying involvement of deep penetrating small vessels.[48] PVSs function as a part of brain clearance system that drains interstitial fluid and solutes including Aβ from brain parenchyma.[48] It is believed that MRI-visible PVSs at CSO might indicate impairment in clearance system resulting in Aβ accumulation at superficial cortical and leptomeningeal vessels in CAA.[48]

Cerebral microinfarcts

Cortical microinfarcts (CMIs) are hyperintense lesions with a greatest dimension less than 5 mm on high resolution T2-weighted imaging studies (3- and 7-Tesla MRI) that are located within the cortical ribbon [Figure 2(d)].[28] Along with CMBs, CMIs are an imaging feature of severe CAA.[28] CMIs appear more frequently in patients with CAA having a more severe amyloid burden, compared with patients with AD and healthy population.[49]

Other MRI findings

There are other MRI features, including lobar lacunes and progressive brain atrophy, suggested to have an association with CAA, although further studies are needed to determine their significance.[17,50–52]

Lacunar infarcts are CSF-filled cavities with a diameter ranging from 3 mm to 15 mm.[20] They could be differentiated from PVSs on MRI by having larger diameters and frequently showing a hyperintense rim on T2-FLAIR sequences [Figure 2(c)].[20] Recent studies have shown that lobar lacunes, which are located at CSO and cortico-subcortical areas, appear more commonly in CAA [Figure 2(c)] while deep lacunes (mainly in the basal ganglia, internal and external capsule, and thalamus) are associated with hypertensive vasculopathy.[50,51] A possible association between lobar lacunes and CAA was supported by another study revealing that the number of lobar lacunes correlate with cerebral amyloid load measured by amyloid-PET.[51]

Brain atrophy refers to low brain volume that may be detected by enlarged CSF spaces due to intracranial volume loss on brain imaging studies.[20] It is better revealed by longitudinal observation [Figure 2(e)].[20] A previous study showed that both sporadic and hereditary CAA is related to cortical atrophy, especially in occipital, temporal, posterior parietal and medial frontal regions that correspond to areas having higher vascular amyloid burden.[52] This finding was also found in patients with Dutch type hereditary CAA (HCHWA-D), supporting the hypothesis that amyloid-related vasculopathy can directly lead to cortical atrophy and dementia independent of AD pathology.[17,52] Functional MRI showing a negative association between vascular reactivity and degree of cortical atrophy provides further evidence between CAA and progressive brain atrophy.[52]

CT features of CAA-ICH

Currently, MRI study is the most informative tool in diagnosing CAA.[19] However, a complete MRI study requires longer examination time and is less suitable to serve as first-line examination tool in emergency setting. Patients with certain conditions, such as having MRI-incompatible pacemaker, are unable to receive MRI studies.[53] Furthermore, MRI is a relatively expensive tool and may not be approachable in countries lacking medical resources.[54]

The brain computed tomography (CT) scan commonly serves as the first imaging study when stroke is suspected.[54] It is widely available, takes shorter time in examination, and requires less economic costs.[53] In addition to the well-known lobar location in CAA-related ICH, one study found that the ICH is more likely to have subarachnoid space extension, an irregular ICH border and multiple ICH episodes on CT [Figure 1(a)].[54] Recently, Edinburgh CT and genetic diagnostic criteria have been proposed.[53] The diagnostic criteria incorporated the possession of an ApoE $\varepsilon 4$ genotype as well as CT findings

including subarachnoid hemorrhage (SAH) and finger-like projections of hematoma border. The prediction model shows excellent discrimination for CAA in the study, but still requires further external validation.[53]

Functional imaging in CAA

While conventional structural imaging studies reveal anatomical alterations in CAA, functional imaging studies yield information about vessel physiological changes which are helpful in understanding the pathophysiology of CAA. These imaging modalities may potentially serve as biomarkers in monitoring treatment responses.[6]

Altered cerebrovascular reactivity

In CAA, the amyloid deposition at vessel walls causes endothelial dysfunction, BBB disruption and impaired vessel autoregulation.[1] These injuries decrease vascular compliances and vessel reactivities to physiological stimulation and may lead to chronic brain tissue ischemia.[1]

Functional MRI measuring responses of blood oxygen level-dependent (BOLD) signals to visual stimulation is a commonly used method to investigate vessel reactivities in CAA.[55] Previous studies have shown that the amplitude of BOLD signals responding to visual stimulation were decreased, and the reaction time were prolonged in patients with CAA compared with healthy elderly people.[55] The reduced BOLD signals in CAA had a gradient distribution with more severe involvement at occipital areas, corresponding to the pathology of occipital predominant amyloid deposition in CAA.[56] The decrement of BOLD signal amplitude correlated to the amounts of WMHs and CMBs, and the responses of BOLD signal significantly worsen in patients with CAA at 1-year follow up, suggesting an association between impairment in vascular reactivities and CAA severity.[56,57]

Microstructural alterations

Diffusion tension imaging study is a measure that enables us to reconstruct whole brain white matter tract and provide information about microstructural changes and global network efficiency.[58] The association between brain connectivity and CAA was supported by studies showing that global network efficiency in patients with CAA was reduced compared with healthy elderly people.[58] Fibers predominantly connecting to occipital and posterior temporal areas were disrupted, which also correlated to the distribution of amyloid burden demonstrated by PET in this study.[58] In longitudinal follow up, the declination rate of brain network efficiency became faster as the severity of CAA increased.[59] The microstructural alteration in CAA may result in impairment of executive function, slow processing speed, and gait disturbance.[58,59]

Molecular imaging of CAA

Molecular imaging study provides information about disease mechanism, functional status and pathological changes by direct labeling of pathologic proteins in brain. Amyloid-PET in CAA has been performed with radiotracers of ^{11}C-Pittsburgh compound B (PiB) or ^{18}F-florbetapir (^{18}F), which directly bind to fibrillar Aβ.[60] With these ligands, PET study is able *in vivo* to detect and quantify amyloid deposition at brain parenchyma and vessels (Figure 3).[60] Tau is another protein that has been reported in CAA but with unclear role.[61] There was only one case-series, using tau-PET with radiotracers of ^{18}F-AV-1451, to discuss tau protein in CAA.[61]

Amyloid-PET

The accuracy and diagnostic utility of amyloid-PET in detecting CAA were investigated in several studies.[60,62,63] Compared to nondemented healthy elderly people and patients with hypertensive ICH, patients with probable CAA had higher global amyloid-PET burden (Figure 3).[63] The diagnostic sensitivity could achieve 77% to 92%, but the specificity was estimated at 66% to 88%.[60,62] The relatively low specificity may be attributed to a possible subclinical AD or age-related parenchyma amyloid deposition because the radiotracers bind to both the vessels and brain parenchyma.[60]

The different tracer uptake pattern of amyloid-PET between CAA and AD has also been investigated but with the limitation of a small sample size and an uncertain clinical significance. Studies have shown that compared with AD, CAA seemed to possess a higher occipital to global amyloid uptake ratio.[60,63,64] This result may correlate to its hallmark pathology of posterior predominant amyloid deposition (Figure 3).

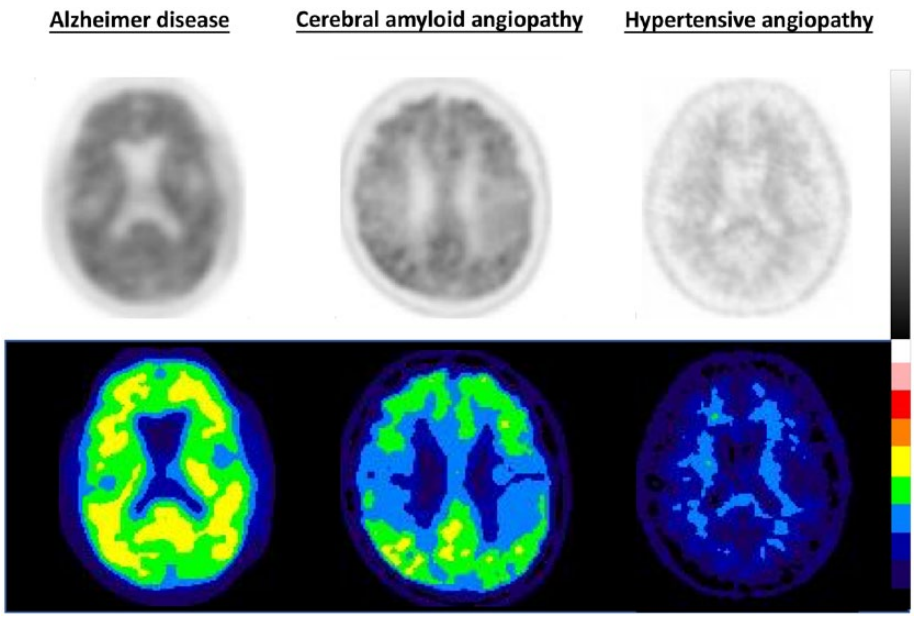

Figure 3. Amyloid-PET in cerebral amyloid angiopathy.
PiB PET in patients with CAA, AD and hypertensive angiopathy. In contrast with patients with hypertensive angiopathy who do not have increased PiB uptake, patients with CAA and AD have higher global PiB retention. Compared with patients with AD, PiB distribution in CAA has a posterior predominant pattern.
AD, Alzheimer's disease; CAA, cerebral amyloid angiopathy; PET, positron emission tomography; PiB, ^{11}C-Pittsburgh compound B.

Amyloid-PET is an useful tool in studying pathophysiology of CAA for its *in vivo* detection of vascular amyloid without having to perform brain biopsy or autopsy.[60] Previous studies showed that CAA patients may develop new ICH or CMBs at locations with greater PiB retention, suggesting that vessels with higher amyloid burden are at larger risk to rupture and cause subsequent hemorrhagic events.[25,26] Other studies also discovered that, among patients with subcortical vascular cognitive impairment, cSS only developed in those who had increased global PiB retention.[65] Patients with cSS or cSAH had higher amyloid burden than those without cSS, supporting that cSS and cSAH may be related to underlying vascular amyloid.[65,66]

Besides hemorrhagic events, amyloid-PET also provides information about CAA-related ischemic changes. It was found that the degree of global PiB uptake was correlated with the volume of WMHs in CAA, but not in AD or healthy elderly people.[67] Another study using PiB PET in primary ICH patients demonstrated that lobar lacune is related to PiB retention and suggested a relationship between lobar lacune and CAA.[51]

Early-phase PiB uptake has been reported as a potential marker to reflect regional brain perfusion and corresponds to brain energy metabolism. A pilot study showed that in CAA, global early-phase PiB uptake was significantly reduced compared with healthy elderly people,[68] but the research and clinical value still requires further validation.

Tau-PET

The exact role of tau protein in CAA is still unknown. A study revealed abnormal phosphorylated tau aggregating around amyloid-laden vessels.[61] Using tau-PET, one case-series reported three patients with probable CAA having CMBs or cSS at areas with increased tau accumulation.[61] Further studies are warranted to confirm this finding.

Conclusion

In recent decades, rapidly growing imaging markers have been developed for studying CAA. Conventional CT and MRI studies are able to reveal anatomical alterations and brain

parenchymal damage. Beyond structural changes, functional MRI and molecular imaging studies provide information about underlying pathophysiology in various disease stages. Combining various imaging technique help us understand CAA in a more comprehensive perspective. These advanced imaging measures are potentially able to detect CAA in an earlier stage and serve as reliable outcome marker in future CAA clinical trials.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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