Cerebral amyloid angiopathy: one single entity?

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Purpose of review
Cerebral amyloid angiopathy (CAA) is a common brain disorder among the elderly and individuals with Alzheimer's disease, where accumulation of amyloid-ß can lead to intracerebral hemorrhage and dementia. This review discusses recent developments in understanding the pathophysiology and phenotypes of CAA.

Recent findings
CAA has a long preclinical phase starting decades before symptoms emerge. Its pathophysiology follows consecutive stages of amyloid-ß deposition, decreased vascular reactivity, nonhemorrhagic changes, and ultimately hemorrhages. Although impaired perivascular clearance is the leading hypothesis underlying CAA, several lines of evidence suggest that glymphatic dysfunction also plays a significant role in the disease process. Despite its common pathway, the disease course is variable. Some patients develop more microbleeds, while others develop larger hemorrhages, suggesting a differentiation in vascular remodeling. Some patients with CAA develop a symptomatic immune response, and inflammation could be an important contributor to vascular damage in CAA in general. Furthermore, the prion-like transmission of amyloid-β has been identified as a cause of iatrogenic CAA occurring decades after neurosurgical procedures involving cadaveric dura mater.

Summary
Emerging evidence of sporadic, hereditary, inflammatory, and iatrogenic CAA suggests a complex interplay between brain clearance, inflammation and vascular remodeling leading to a diverse clinical phenotype.

Keywords
cerebral amyloid angiopathy related inflammation, cerebral amyloid angiopathy, iatrogenic cerebral amyloid angiopathy, intracerebral hemorrhage

INTRODUCTION

Current neurological practice acknowledges cerebral amyloid angiopathy (CAA) as one of the main causes of spontaneous (lobar) intracerebral hemorrhage (ICH) and vascular dementia worldwide [1]. A recent study estimated that CAA is present in 48% of Alzheimer's disease patients and 57% of those with lobar ICH [1]. The disease is caused by the deposition of the protein amyloid-ß in the walls of the cortical and leptomeningeal blood vessels of the brain, leading to decreased vascular reactivity, vessel remodeling and rupture [2,3▪▪]. Recently, prospective data from patients with hereditary (Dutch-type) CAA were used to formulate a pathophysiological model describing the supposed steps in the disease course [4▪▪]. Similar to Alzheimer's disease, the gold standard for diagnosing CAA is still histopathological analysis of biopsy samples or brain autopsy. The widely used Boston criteria, define probable CAA based on clinical symptoms and brain MRI findings, allowing a noninvasive in vivo diagnosis. Published in 2022, the Boston criteria v2.0 include new MRI markers (i.e. enlarged perivascular spaces in the centrum semiovale and white matter lesions in a multispot pattern), enhancing sensitivity while maintaining specificity. The Boston 2.0 criteria can be applied in patients of 50 years and older who present with ICH, cognitive decline, or transient focal neurological episodes (sometimes referred to as 'amyloid spells'). As was discussed in the previous review on CAA for this journal, patients with CAA present with a spectrum of clinical symptoms, and CAA might be considered a multiphenotype disease due to the significant variability among

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KEY POINTS

- Cerebral amyloid angiopathy (CAA) is a disease with a decade long preclinical course and follows consecutive pathophysiological phases with amyloid deposition, loss of vasoreactivity, nonhemorrhagic injury (associated with white matter lesions), and hemorrhagic lesions (cerebral microbleeds, symptomatic intracerebral hemorrhage, cortical superficial siderosis, or convexity subarachnoid hemorrhage).
- Some patients with CAA may develop a large intracerebral hemorrhages, while others mainly develop microbleeds and microinfarctions, possibly reflecting different pathophysiological processes and varying risks of bleeding.
- Early immunosuppressive treatment may improve the disease course of patients with CAA-ri and reduce the risk of CAA-ri recurrence.
- Prion-like transmission of amyloid-β via cadaveric dura can cause iatrogenic CAA decades after neurosurgery; therefore, clinicians should consider the possibility of an iatrogenic cause when diagnosing CAA patients.

patients [5,6]. The aim of this review is to discuss new developments and insight into the different entities of the CAA spectrum.

PATHOPHYSIOLOGIC EVIDENCE FOR DIFFERENT ENTITIES

Deposits of amyloid-ß protein in the walls of small cerebral arteries are typically asymptomatic, but can cause hemorrhages and microinfarcts in advanced cases. Although it has now been long acknowledged that it is the vascular deposition of the amyloid-ß that seems to be the earliest sign of CAA, not much is known about the process leading to this initial deposition [4▪▪]. Amyloid deposition in brain capillaries is classified as CAA type I and is associated with neuritic plaques and Alzheimer's pathology, whereas noncapillary CAA (CAA type II) is more related to hemorrhages [2]. Aβ42 has been hypothesized to seed in the vessel walls, initiating vascular Aβ accumulation, which is then expanded by Aβ40 deposition [7]. Furthermore, histopathological studies have demonstrated that different processes can follow after this initial deposition in the vessel wall [8]. This amyloid-ß deposition can lead to a process of vessel remodeling, where two different forms of remodeling have been described: Vonsattel stage III, concentric splitting of the vessel wall (also called 'vessel-within-vessel' appearance) is a histopathological finding strongly related to ICH and cortical superficial siderosis (cSS) [9]. Another form of vessel remodeling, Vonsattel stage IV, characterized by loss of amyloid-β locally with replacement of the arteriolar wall with fibrinoid material, is contrastingly more strongly related to microbleeds [10]. It is currently thought that these types of remodeling are different possible outcomes of initial amyloid deposition, possibly influenced by factors such as regional inflammation [8]. Vessels occluded with amyloid, but without remodeling, are often found to underly microinfarctions and white matter hyperintensities, lesions strongly related to cognitive decline in CAA [10]. Parenchymal or cortical damage resulting from initial amyloid-ß deposition can thus be both hemorrhagic or ischemic in nature. These different possible pathways might be an explanation for the heterogeneity seen in clinical disease expression. Although the recently formulated framework does not yet include these possible pathways, future studies must include them in order to fully understand CAA pathophysiology.

MACROBLEED VS. MICROBLEED PREDOMINANCE

Patients with CAA related ICH have a high hemorrhage recurrence rate. Studies have shown that ICH is strongly related to presence of cSS, with cSS being the strongest predicting factor for (recurrent) ICH [11]. cSS and microbleeds are furthermore thought to be a cause of transient focal neurological episodes: attacks of spreading positive or negative neurological symptoms often seen in patients with CAA [12]. However, not all patients with CAA suffer from ICH, nor do all patients have evidence of cSS on MRI; a subtype of CAA patients seem to present primarily with cognitive decline and extensive lobar microbleeds, with multiple cortical microinfarctions on MRI [13,14]. Both ICH and cSS are related to the APOE-e2 genotype [5]. In contrast, the APOE-e4 genotype is more strongly related to CAA without ICH. On a cellular level, APOE-e4 is related to capillary CAA, a finding also frequently seen in patients with Alzheimer's disease and for which APOE-e4 is also a strong risk factor, whereas APOE-e2 is related to CAA without capillary CAA [2]. Lastly, histopathological studies have demonstrated that different pathophysiological processes are thought to underly micro- and macrobleeds (the last often presenting as symptomatic ICH), demonstrating that microbleeds often have underlying Vonsattel grade IV vessel remodeling, whereas cSS and ICH more often are related to Vonsattel grade III [15]. Clinically CAA is often considered to be either mainly presenting with hemorrhage related symptoms, cognitive symptoms, or transient focal neurological episodes, and

it might furthermore be added that patients with CAA could possibly be considered to be 'macro' bleeders or mainly 'micro' bleeders, based on the evidence mentioned above. Caution is advised, however, against considering these two phenotypes as completely separate entities, and they should instead be viewed as possible opposite ends of the CAA disease spectrum.

IMPLICATIONS FOR CLINICAL MANAGEMENT

Currently there is not yet any available, effective and safe treatment for CAA. As previously discussed, managing blood pressure and avoiding anticoagulant use are of utmost importance for all patients with CAA [6]. These factors should be even more strictly managed in those patients with previous ICH and cSS on MRI. Evidence as mentioned above for possible phenotypes in CAA impacts this management, as the risk of future ICH seems to be higher in the abovementioned 'macro' bleeders vs. the 'micro' bleeders. Besides, with the growing use of brain MRI for various indications, microbleeds are often detected in patients without cortical cSS or ICH. When antithrombotics or anticoagulants are otherwise indicated (e.g. for stroke prevention), the presence of microbleeds alone should not be a barrier to their use [16]. However, when use of antithrombotics or anticoagulants poses too much risk, alternative treatments for diseases such as atrial fibrillation (in the form of left atrial appendage closing) should be considered in this group, and use of anticoagulants for diseases such as venous thrombosis should only be used in life threatening situations and for the shortest duration possible [17].

Future studies are planned investigating other amyloid modifying pathways, such as DNA and RNA targeting therapies, however these are still in the early trial phases [29].

CEREBRAL AMYLOID ANGIOPATHY RELATED INFLAMMATION

The immune system is increasingly recognized to play a role in CAA related damage. As in other chronic brain diseases, inflammation is frequently observed in CAA, but whether it is an epiphenomenon or a cause of vascular damage remains unclear.

Inflammation has long been observed in patients with CAA-related inflammation (CAA-ri), where inflammation around and within blood vessels leads to blood–brain barrier (BBB) leakage and vessel rupture [18]. As a result of this, patients with CAA-ri can present with a severe subacute encephalopathy sometimes accompanied by seizures or with milder focal neurological symptoms, an altered cognitive state, and/or headache. Brain MRI typically demonstrates asymmetrical white matter hyperintensities suggestive of vasogenic edema on T2-weighted images, along with cortical and subcortical hemorrhagic lesions on SWI or GRE sequences, allowing a diagnosis without requiring a brain biopsy [19]. Regions of vasogenic edema often seem to co-localize with cerebral microbleeds, and although this is not mandatory for the diagnosis this also implies a link between vessel rupture and local inflammation [20].

In patients with a history of CAA presenting with subacute neurological deficits, diagnosing CAA-ri does not have to be difficult when the clinicoradiological criteria proposed by Auriel *et al*. are used [19]. However, when the differential diagnosis is broader than CAA with or without inflammation, the diagnostic process becomes more complex. In such cases, it's essential to acknowledge the limited test accuracy of these criteria, particularly in the 'possible' CAA-ri category (with sensitivity of 82% and a specificity of 68%). The fact that these criteria were validated in a cohort of patients with pathologically confirmed CAA-ri and patients with CAA without inflammation as a control group, makes them less reliable for distinguishing CAA-ri from CAA mimics. In that case, a cerebrospinal fluid (CSF) study can be performed to explore evidence for alternative diagnoses. Besides, the clinicoradiological criteria are set an age limit of 40 years, although clinical experience suggests that CAA-ri is rare in individuals under 50. Especially in younger patients, primary angiitis of the central nervous system (PACNS) is sometimes mistaken for CAA-ri. A recent study highlighted that clinical and brain MRI features differ between CAA-ri and PACNS, which can assist clinicians in making more accurate diagnoses [21].

In addition, an increasing line of evidence is supporting a link between CAA and inflammation in patients without evident CAA-ri [22▪]. Studies in animal models have shown that perivascular macrophages may influence CAA severity and might contribute to clearing amyloid-ß from cerebral vasculature [23,24]. In histopathology samples of severe CAA cases, perivascular inflammation (characterized by reactive astrocytes and activated microglia) was predominantly observed around arterioles with severe CAA pathology. These findings suggest that perivascular inflammation and BBB leakage may contribute to arteriolar remodeling and hemorrhage in CAA [9].

The significance of inflammation and CAA has grown substantially with the implementation of immunotherapies for Alzheimer's disease [25]. Presence of CAA has been associated with adverse reactions to these antiamyloid immunotherapies, termed amyloid-related imaging abnormalities (ARIA). CAA-ri shares clinical and radiological similarities with ARIA, which involves ARIA-E (edema) and ARIA-H

(hemorrhage), representative of vascular inflammation and vessel weakening in the brain [26]. Besides CAA, ARIA's risk is associated with the APOEe4 allele, and immunotherapy dosage, and it often shows phagocytic reactions at Aβ-accumulated vessels [2,27]. More research into the pathophysiology of ARIA and the development of reliable biomarkers to predict ARIA related complications is needed to mitigate the risks of these new treatments.

Patients presenting with CAA-ri often respond well to immunosuppressive therapy. The effect of immunosuppressive therapy for CAA-ri has been supported by a retrospective cohort study of 48 patients, suggesting that treating patients early may improve the disease course of CAA-ri and lower the risk of CAA-ri recurrence [28]. Whether targeting the immune system can effectively treat other patients with CAA to lower the risk of ICH and slow cognitive decline remains to be determined. Although initial efforts are underway [DOI: 10.1186/s13063-023-07371-4], there is need for further studies on this topic.

Therefore, current methods for CAA management mainly focus on preventing ICH.

IATROGENIC CAA

CAA has long been considered a disease of the elderly. Although several rare hereditary variants exist, most patients with CAA present after the fifth decade [30]. Recently, however, a growing group of 'young' patients with CAA (i.e., too young to fulfill the Boston criteria 2.0) has been identified. These patients developed severe CAA three to four decades after childhood neurosurgery involving the use of cadaveric dura material, after receiving cadaver-derived growth hormone, or following a red blood cell transfusion as infants [31,32▪,33]. Diagnostic criteria for iatrogenic CAA (iCAA) in adults under 55 have been proposed [31]. Based on an age of onset below 55 (using the same age cut-off as the previous Boston Criteria for CAA), a history of potential exposure (such as procedures using cadaveric human brain tissue, pituitary-derived hormones, or relevant neurosurgical procedures), radiological findings and clinical symptoms suggestive of CAA, the accumulation of amyloid-β (Aβ) (confirmed through PET imaging, CSF analysis, or brain biopsy), and the exclusion of genetic causes, the diagnosis can be suggested. However, external validation of these criteria has not yet been performed, and therefore, the diagnostic performance remains unknown.

In addition, possible iatrogenic CAA has been recently identified in adults aged 65 and older, all of whom had undergone previous neurosurgical procedures, widening the age range [34]. The hypothesis that CAA can be caused by prion-like transmission from amyloid-β in cadaveric material is novel, but the exact pathways need further investigation, as they could shed light on the still unknown mechanisms of initial amyloid deposition in CAA [32▪].

Determining the exact number of exposed individuals is challenging due to inconsistencies in record-keeping. It is unclear how many patients have undergone neurosurgical procedures during which cadaveric dura mater was used and how many may develop iCAA. Although the use of cadaveric human material has been restricted in most countries since 1990 due to the risk of iatrogenic Creutzfeldt–Jakob disease, clinicians treating patients with CAA are still advised to be aware of potential iatrogenic causes, even in patients who develop CAA after the age of 50. These questions about exposure and risk of developing iCAA are currently being addressed in an international registry [35], and clinicians who encounter a suspected iatrogenic CAA case are advised to consult with a CAA referral center.

CONCLUSION

Based on the evidence presented above we consider CAA to be one disease with a long preclinical phase and with multiple possible presenting clinical and radiological phenotypes (see Fig. 1). CAA is in all cases thought to be caused by the initial deposition of the protein amyloid-ß in the small vessels of the brain. This might happen through either a 'seeding' of amyloid-ß, alterations of the amyloid-ß protein due to a genetic mutation, or yet to be uncovered processes possibly related to aging. However, depending on where the protein is deposited (capillary vs. no capillary involvement), if the deposition triggers any auto-inflammatory response, and if initial deposition leads to eventual vessel remodeling seems to determine the clinical signs and symptoms of the presenting patient (hemorrhagic vs. nonhemorrhagic). We caution, however, against viewing the different phenotypes of CAA mentioned above as distinct subtypes. We would instead advise to consider CAA a spectrum, in which patients can present with different phenotypes but in which much overlap can be seen. Possible factors influencing CAA phenotype might include APOE genotype, cardiovascular risk factors (such as hypertension), and sex [17,36,37]. Further research should investigate whether these insight into the pathophysiology can be used to create new treatment strategies and slow down the disease progression of patients with CAA.

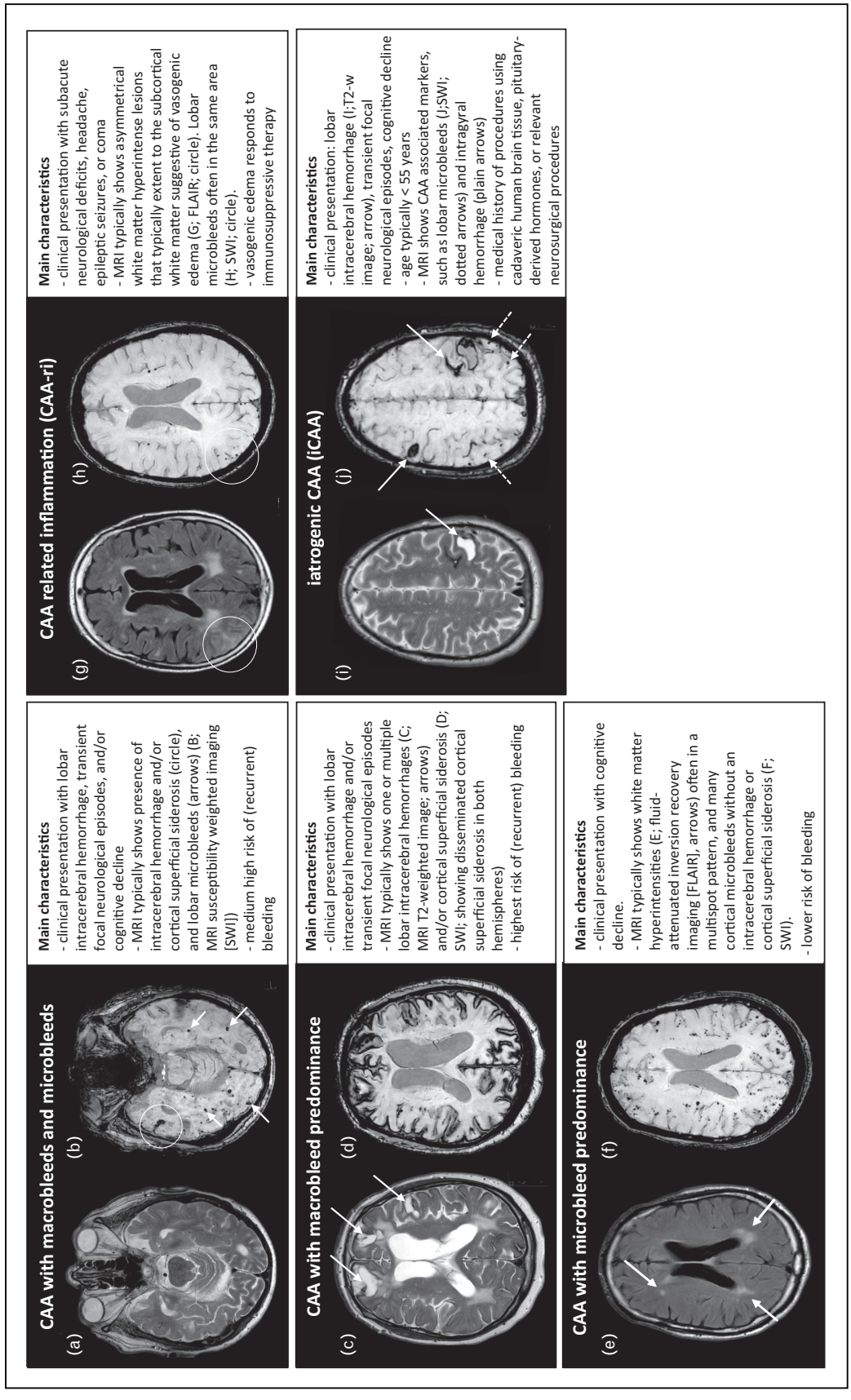

FIGURE 1. Different clinical and radiological CAA phenotypes. CAA, cerebral amyloid angiopathy.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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