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Cerebral Amyloid Angiopathy: Emerging Evidence for Novel Pathophysiology and Pathogenesis

Masahito Yamada, Kenji Sakai, Tsuyoshi Hamaguchi, and Moeko Noguchi-Shinohara

Abstract

Cerebral amyloid angiopathy (CAA) is cerebrovascular amyloid deposition being classified into several types according to the amyloid protein involved. Of these, sporadic amyloid β-protein (Aβ)-type CAA is most commonly found in older individuals and in patients with Alzheimer's disease (AD). Cerebral blood vessels affected with CAA are associated with functional and pathological changes (CAA-associated vasculopathies), leading to development of hemorrhagic disorders (lobar intracerebral macrohemorrhage, cortical microhemorrhage, and cortical superficial siderosis/focal convexity subarachnoid hemorrhage), ischemic disorders (white matter disease and cortical microinfarcts), and inflammatory vascular disorders, i.e., CAA-associated inflammation/angiitis; these CAA-related disorders are characterized by unique clinical features and imaging and cerebrospinal fluid abnormalities, contributing to a clinical diagnosis of CAA without brain biopsy. In this review, we particularly focus on topics with emerging evidence for novel pathophysiology and pathogenesis of CAA. They include CAA-related cognitive impairment and neurodegeneration, and CAA-related inflammation and similar disorders associated with Aβ immunotherapies for AD. Furthermore, recent studies indicated that Aβ pathologies, including CAA, would be transmissible in humans as well as experimental settings. Better understanding of mechanisms underlying pathophysiology and pathogenesis of CAA would lead to new strategies for interventions for CAA.

Abbreviations

Aβ	amyloid β-protein
AβPP	β-amyloid precursor protein
ACE	angiotensin-converting enzyme
ACT	α1-antichymotrypsin
ACys	amyloid cystatin C
AD	Alzheimer's disease
AGel	amyloid gelsolin
AL	amyloid immunoglobulin light chain
APOE	apolipoprotein E
APOE	apolipoprotein E gene
APrP	amyloid prion protein
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid-related imaging abnormalities-vasogenic edema and sulcal effusions
ARIA-H	amyloid-related imaging abnormalities -microhemorrhages and hemosiderin deposits

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S.-H. Lee (ed.), *Stroke Revisited: Pathophysiology of Stroke*, Stroke Revisited,
https://doi.org/10.1007/978-981-10-1430-7_7

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ATTR	amyloid transthyretin
BOLD	blood-oxygen-level-dependent
CAA	cerebral amyloid angiopathy
CAA-ri	cerebral amyloid angiopathy-related inflammation
CBF	cerebral blood flow
CJD	Creutzfeldt–Jakob disease
CMB	cerebral microbleed
cSAH	convexity subarachnoid hemorrhage
CSF	cerebrospinal fluid
cSS	cortical superficial siderosis
dCJD	dura mater graft-associated Creutzfeldt–Jakob disease
DMT	disease-modifying therapies
FDG	fluorodeoxyglucose
FLAIR	fluid attenuation inversion recovery
fMRI	functional MRI
hGH	human cadaveric pituitary-derived growth hormone
ICH	intracerebral hemorrhage
iCJD	iatrogenic CJD
LRP-1	low-density lipoprotein-receptor related protein
MB	microbleed
MCI	mild cognitive impairment
PiB	Pittsburgh Compound B
PS1	presenilin 1
p-tau	phosphorylated tau
p-TDP-43	phosphorylated transactive response DNA binding protein 43 kDa
SAH	subarachnoid hemorrhage
sCJD	sporadic Creutzfeldt-Jakob disease
SVD	small vessel disease
TDP-43	transactive response DNA binding protein 43 kDa
TGF-β1	Another CAA-related gene reported by more than one research group transforming growth factor-β1
VaD	vascular dementia
WMH	white matter hyperintensity

7.1 Introduction

Cerebral amyloid angiopathy (CAA) is cerebrovascular amyloid deposition, and is classified into several types according to the amyloid protein involved (Table 7.1). So far, seven amyloid proteins have been reported in CAA including amyloid β-protein (Aβ), cystatin C (ACys), prion protein (APrP), ABri/ADan, transthyretin (ATTR), gelsolin (AGel), and, rarely, immunoglobulin light chain amyloid (AL); among these, sporadic CAA of the Aβ type is most commonly found in older individuals as well as in patients with Alzheimer's disease (AD) (see reviews [1–3]). This chapter reviews sporadic Aβ-type CAA focusing on emerging evidence for novel aspects of pathophysiology and pathogenesis, such as CAA-related neurodegeneration and inflammation, and transmission of Aβ pathology.

7.2 Sporadic Aβ-Type CAA: General Aspects

Sporadic Aβ-type CAA occurs in approximately a half of older individuals showing an increase of the prevalence of CAA with age. Figure 7.1 shows the prevalence of CAA in AD and non-AD subjects. CAA is commonly observed in AD with higher prevalence of 80–90% and higher severity compared with non-AD subjects [2]. In this section, we briefly describe general aspects of sporadic Aβ-type CAA including pathogenesis and pathophysiology, risk factors, CAA-related cerebrovascular disorders, biomarkers, and diagnosis (see review [3]).

7.2.1 Pathology, Pathogenesis, and Pathophysiology

CAA is observed mainly in the leptomeningeal and cortical vessels of the cerebral lobes and cerebellum. The occipital lobe is preferentially affected, whereas CAA is uncommon in the basal ganglia, thalamus, brainstem, and white matter. Mild CAA is almost silent clinically, while, in severe CAA, most of small arteries and arterioles are affected with marked amyloid deposition, associated with degeneration of smooth muscle cells and other vasculopathic changes leading to CAA-related cerebrovascular disorders. Amyloid deposits in capillaries and, occasionally, in arterioles or small arteries appear to infiltrate the surrounding parenchymal tissue, and accompany dystrophic neurites forming plaque-like structures (drüsige Entartung/angiopathie dyshorique). CAA in capillaries has been referred to

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Table 7.1 Classification of cerebral amyloid angiopathy (CAA)

Amyloid protein	Clinical phenotype
1. Amyloid β-protein (Aβ)	1. Sporadic; associated with: (a) Aging (b) Sporadic Alzheimer's disease (AD) (c) Other conditions, including vascular malformations, irradiation
	2. Hereditary or genetic; associated with: (a) Mutations in the amyloid β-protein precursor (AβPP) gene, including hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D) E693Q, E693K (Italian), E693G (Arctic), A692Q (Flemish), E694N (Iowa), L705V (Piedmont), A713T (Italian), and AβPP gene duplication. (b) Mutations of presenilin genes (c) Down syndrome
2. Cystatin C (ACys)	HCHWA-Icelandic type (HCHWA-I) associated with a mutation (68Leu → Gln) of the cystatin C gene
3. Prion protein (PrP) (APrP)	Prion disease associated with mutations of the PRNP gene (Y145Stop, Y163Stop, Y226Stop)
4. ABri/ADan	Familial British or Danish dementia (FBD/FDD) associated with mutations of the BRI gene
5. Transthyretin (ATTR)	Meningocerebrovascular involvement of familial transthyretin (TTR) amyloidoses (familial oculoleptomeningeal amyloidosis, familial amyloid polyneuropathy) associated with mutations of the TTR gene
6. Gelsolin (AGel)	Meningocerebrovascular involvement of gelsolin-related amyloidosis (familial amyloidosis, Finnish type) associated with mutations of the gelsolin gene
7. Immunoglobulin light chain amyloid (AL)	CAA with leukoencephalopathy due to brain-restricted monoclonal plasma cell proliferation

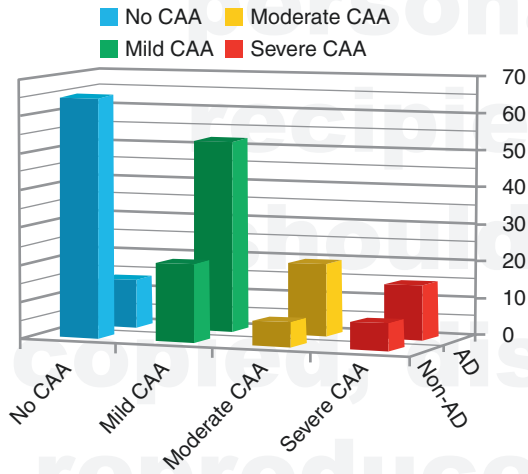

Fig. 7.1 The distribution of the severity of cerebral amyloid angiopathy (CAA) in elderly individuals (n = 201; age, 85.9 ± 8.0 years) with and without Alzheimer's disease (AD), from our autopsy series including AD (n = 82; age, 86.1 ± 7.9 years) and non-AD cases (n = 119; age, 85.7 ± 8.0 years). (Cited from the reference [2])

as "capillary CAA (CAA-Type 1)," to distinguish it from non-capillary CAA (CAA-Type 2). CAA-associated vasculopathies include duplication ("double-barrel" lumen), obliterative intimal changes, hyaline degeneration, microaneurysmal dilatation, and fibrinoid necrosis.

How does Aβ deposit in walls of cerebral blood vessels? Aβ cleaved from the β-amyloid precursor protein (AβPP) by β-secretase and β-secretase has heterogeneity of the C-terminal; the length of Aβ deposited in senile plaques is mainly 42–43 residues ($Aβ_{42}$), while that of cerebrovascular Aβ (CAA) is mainly 39–40 residues ($Aβ_{40}$) (Fig. 7.2). Aβ in CAA is considered to derive from the brain; after releasing from neurons, $Aβ_{42}$ easily aggregates and deposits in the brain parenchyma as senile plaques; whereas, $Aβ_{40}$ does not aggregate so easily as $Aβ_{42}$, and is transported, through perivascular interstitial fluid drainage pathways, for clearance. In this process, $Aβ_{40}$ aggregates on vascular basement membranes [1].

The pathophysiology of Aβ-type CAA is shown in Fig. 7.3. CAA-associated vasculopathies lead to development of hemorrhagic lesions [lobar intracerebral (macro)hemorrhage (ICH), cortical microhemorrhage or microbleed (MB), and cortical superficial siderosis (cSS)/focal convexity subarachnoid hemorrhage (cSAH)], ischemic lesions [cortical infarction and isch-

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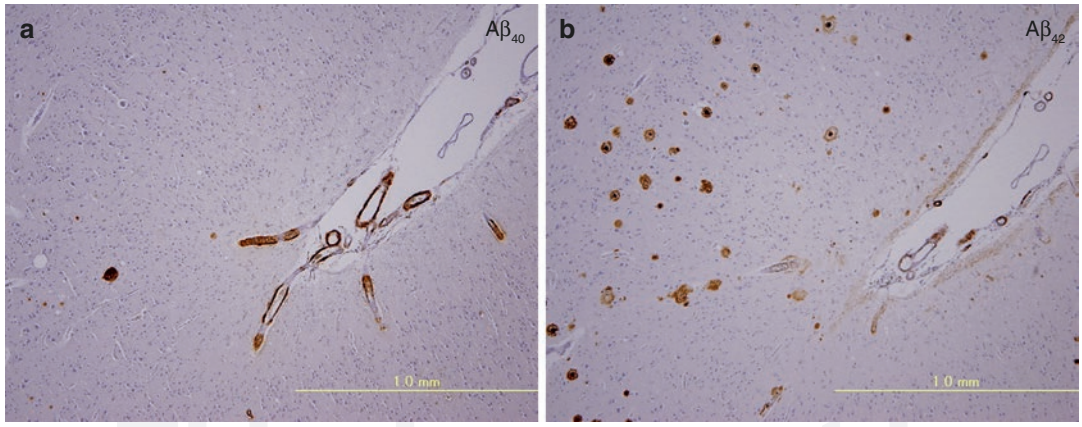

Fig. 7.2 Serial sections of the cerebral cortex immunostained with antibodies to $A\beta_{40}$ (**a**) and $A\beta_{42}$ (**b**). A major component of cerebrovascular amyloid is $A\beta_{40}$, while, that of parenchymal amyloid (plaques) is $A\beta_{42}$

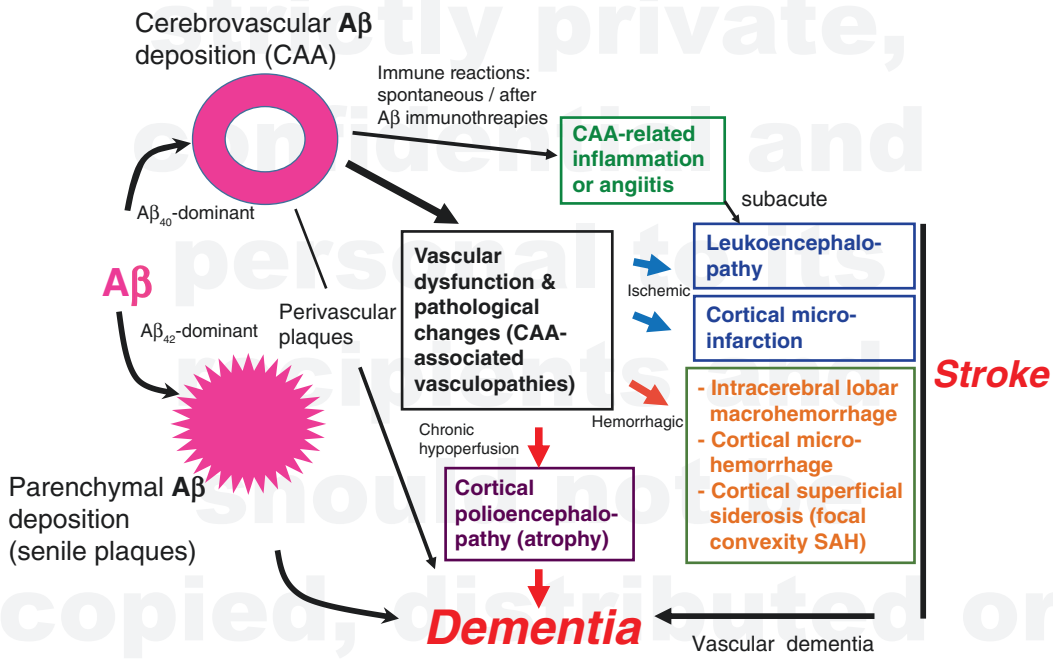

Fig. 7.3 Pathophysiology of cerebral amyloid angiopathy (CAA) and CAA-related disorders. Aβ shows parenchymal (senile plaques) or vascular deposition (CAA), depending on dominance of $A\beta_{42}$ or $A\beta_{40}$, respectively. CAA is related to stroke and dementia. (Modified from the reference [3])

emic changes of the white matter (leukoencephalopathy)], cortical polioencephalopathy (atrophy), and subacute leukoencephalopathy caused by CAA-related inflammation/angiitis. CAA-related disorders as well as coexisting AD pathology contribute to cognitive impairment or dementia. Thus, CAA is related to dementia, stroke, encephalopathies, and dementia.

7.2.2 Risk Factors

Besides aging and AD, some genetic and nongenetic risk factors of CAA and CAA-related disorders have been reported.

The apolipoprotein E (APOE) gene (*APOE*) has been reported to be a risk factor for sporadic CAA as well as AD; the ε4 allele for CAA itself,

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and the ε2 allele for CAA-related ICH. The *APOE* ε2/ε4 genotype was associated with early recurrence of lobar ICH in patients who survived a lobar ICH. The *APOE* ε4 allele is risk for capillary CAA (CAA-Type 1), CAA-related inflammation, [4] cerebral MBs (CMBs), and CAA in head injury cases, and *APOE* ε2 for cSS. Other genetic factors include polymorphisms in the genes of transforming growth factor (TGF)-β1, presenilin 1 (PS1), α1-antichymotrypsin (ACT), neprilysin, low-density lipoprotein-receptor related protein (LRP-1), angiotensin-converting enzyme (ACE), and CR1.

Some factors increase risk for CAA-related hemorrhages, including hypertension, and thrombolytic, anticoagulation, and antiplatelet therapies [5]. CAA could be a risk factor for ICH with thrombolytic therapies for acute myocardial infarction, pulmonary embolism, or ischemic stroke, and for ICH with warfarin therapies. Thrombolytic or anticoagulation therapies in patients with MBs are potential risk factor for ICH. The *APOE* ε2 and ε4 alleles were reported as strong risk factors for lobar warfarin-related ICH; this association was considered to be mediated by CAA. The use of antiplatelet drugs, such as aspirin, is associated with the presence of MBs, and with strictly lobar MBs suggestive of CAA. A review for antithrombotic (antiplatelet or anticoagulant) therapy for patients with ischemic stroke/transient ischemic attack and cerebral MBs suggested that less than five CMBs should not affect antithrombotic decisions, although with more than five MBs the risks of future ICH and ischemic stroke are finely balanced, and antithrombotics might cause the net harm [5].

7.2.3 CAA-Related Cerebrovascular Disorders

7.2.3.1 Hemorrhagic Disorders

CAA-associated vasculopathies in the cortical and meningeal vessels of cerebral and cerebellar cortices accompany symptomatic lobar ICH, lobar CMBs, and cSS/focal cSAH.

Lobar Intracerebral Hemorrhages/Cortical Microbleeds CAA-related lobar ICH was noted in 12–20% of total ICH cases with a recent increase of its incidence. CAA-related lobar ICH is characterized by multiple and recurrent occurrence and clinical manifestations including motor paresis, disturbance of consciousness, abnormalities in higher brain functions, such as aphasia, visual loss, with headache which is probably related to secondary subarachnoid hemorrhage (SAH), at the acute stage, and dementia and seizures during chronic stages.

With sensitive MR imaging techniques, such as gradient-echo T2∗ imaging and susceptibility-weighted imaging, MBs were found in 47.4% of patients with pathologically confirmed CAA cases [6]. CAA-related MBs are frequently lobar in distribution. Studies with amyloid positron emission tomography (PET) using ^{11}C-Pittsburgh Compound B (PiB) reported close spatial and temporal relationships between lobar MBs and amyloid deposits.

A recent meta-analysis of prospective cohorts following ICH indicated that the annual recurrent ICH risk was higher in CAA-related ICH vs CAA-unrelated ICH [7]. Patients with lobar MBs are at considerable risk of future symptomatic lobar ICH. In the meta-analysis for patients with CAA-related ICH, higher numbers of multiple baseline MBs were associated with higher risk of ICH recurrence during follow-up; however, single MB was not associated with recurrent ICH [7].

Cortical Superficial Siderosis/Focal Convexity Subarachnoid Hemorrhages CAA is a frequent cause of cSS/focal cSAH, a subtype of non-aneurysmal SAH, in patients over the age of 60 and in those with AD [8]. cSS is found in 60.5% of pathologically confirmed CAA cases [6]. Although cSS is associated with lobar MBs, cSS tends to occur in individuals with relatively fewer cortical MBs, suggesting differences in vasculopathic changes between CAA-related MBs and cSS. cSS/cSAH is associated with an increased future risk of bleeding, lobar ICH, or cSAH [9]. Importantly, cSS and cSAH have been reported to present with transient focal neurological episodes (TFNEs), mainly spreading sensory symptoms; TFNEs are a clinical marker of cSS and may be caused by cSS through cortical spreading depression or focal seizure [9]. Antiplatelet or anticoagulant therapies based on the misdiagnosis of CAA-related TFNEs as transient ischemic attacks may induce CAA-related ICH.

7.2.3.2 Ischemic Disorders

CAA-related cerebral hypoperfusion or occlusive small-vessel disease may cause progressive white matter lesions and cortical microinfarcts.

White Matter Disease Patients with CAA-related ICH exhibit occipital dominant white matter hyperintensities (WMHs) on MRI, compatible with predilection of CAA pathology for posterior brain regions. A posterior distribution of WMH on MRI is associated with the presence of CAA pathology, which could be a possible marker of CAA. Amyloid burden in non-demented CAA subjects correlated with WMH volumes.

Cortical Microinfarcts Acute or subacute subclinical ischemic infarcts are common in CAA-related ICH. As a result of the difficulty in detection, CAA as a cause of cortical microinfarcts is underrecognized (see the section of biomarkers).

7.2.4 Biomarkers and Diagnosis

7.2.4.1 Biomarkers

Common Imaging Markers Blood-sensitive MRI techniques, such as gradient-echo T2∗ imaging and susceptibility-weighted imaging, are useful for detection of MBs and cSS. In addition, enlarged perivascular spaces in the centrum semiovale are associated with clinically diagnosed CAA with ICHs, MBs, or cSS, and with pathologically confirmed CAA, suggesting that they could be an MRI marker for CAA [10]. For ischemic lesions, acute or subacute cortical or subcortical infarctions can be recognized in CAA on diffusion-weighted images; however, old cortical microinfarcts are often difficult to detect, probably requiring high-resolution MRI. A high-resolution MRI-histopathological study indicated that MBs on MRI are specific for microhemorrhages in CAA, and that, in contrast, the vast majority of microinfarcts currently remain under the detection limits of clinical in vivo MRI [11].

Functional Imaging Impaired cerbrovascular reactivity in response to visual stimulation was reported in studies with transcranial Doppler ultrasound or functional MRI (fMRI) measuring changes in blood-oxygen-level-dependent (BOLD) signal and regional cerebral blood flow (CBF) using pseudo-continuous arterial spin labeling [12]. Impaired vascular function was detected even in presymptomatic subjects with hereditary CAA of Dutch type [12].

Amyloid PET Amyloid imaging with a PET ligand, ^{11}C-PiB, revealed an increase of PiB binding that often shows greater occipital uptake in CAA-related ICH and is also associated with cortical MBs. Recent studies indicated that ^{18}F-florbetapir, another PET tracer, labeled vascular amyloid in patients with CAA-related ICH, providing a sensitivity of 100% and a specificity of 89% to discriminate CAA-related ICH from hypertensive ICH [13]. The tracers label both parenchymal and vascular amyloid deposits, and amyloid positivity is frequently found in healthy elderly individuals with preclinical AD and patients with clinical AD. Therefore, amyloid PET has low specificity for CAA; however, a negative PiB scan rules out CAA with excellent sensitivity [7].

Biochemical Markers Cerebrospinal fluid (CSF) markers are useful. CSF levels of $A\beta_{40}$ as well as $A\beta_{42}$ show a significant decrease in patients with probable CAA. Decreased CSF levels of $A\beta_{40}$ and $A\beta_{42}$ occur before onset of hereditary CAA of Dutch type in mutation carriers [14]. The findings would reflect trapping of $A\beta_{40}$ and $A\beta_{42}$ in the cerebrovasculature in early steps of CAA pathogenesis. Patients with isolated cSS also showed lower CSF $A\beta_{42}$ and $A\beta_{40}$ levels. CSF levels of total tau and phosphorylated tau are higher in patients with probable CAA than in controls, but lower than in AD. The presence of anti-Aβ autoantibodies in CSF is a marker of CAA-related inflammation (see below) [15].

7.2.4.2 Diagnosis

The Boston criteria were used for the diagnosis of CAA-related ICH (Table 7.2), and high diagnostic accuracy was reported with a small pathologic series [16]. As cSS has been established as a biomarker of CAA, cSS was incorporated into the classic Boston criteria (the modified Boston criteria) (Table 7.2), in which the sensitivity increased from 89.5 to 94.7%, and the specificity was 81.2%

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Table 7.2 Classic[a] [16] and modified Boston criteria [6] for diagnosis of CAA-related hemorrhage

1. Definite CAA Full postmortem examination demonstrating: • Lobar, cortical, or corticosubcortical hemorrhage • Severe CAA with vasculopathy[b] • Absence of other diagnostic lesions
2. 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 the specimen • Absence of other diagnostic lesions
3. 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[c] or disseminated[d] superficial siderosis] • Age ≥55 years • Absence of other causes of hemorrhage [or §superficial siderosis][e]
4. Possible CAA Clinical data and MRI or CT demonstrating: • Single lobar, cortical, or corticosubcortical hemorrhage[or §focal[a] or disseminated[b] superficial siderosis] • Age ≥55 years • Absence of other causes of hemorrhage [or §superficial siderosis][e]

The modified criteria are indicated by §

[a]Criteria established by the Boston Cerebral Amyloid Angiopathy Group: Steven M. Greenberg, MD, PhD, Daniel S. Kanter, MD, Carlos S. Kase, MD, and Michael S. Pessin, MD

[b]As defined in: Vonsattel JP, Myers RH, Hedley-Whyte ET, Ropper AH, Bird ED, Richardson EP Jr. Cerebral amyloid angiopathy without and with cerebral hemorrhages: a comparative histological study. *Ann Neurol* 1991;30: 637–649 [52]

[c]Siderosis restricted to 3 or fewer sulci

[d]Siderosis affecting at least 4 sulci

[e]Other causes of intracerebral hemorrhage: excessive warfarin (international normalization ratio, INR > 3.0); antecedent head trauma or ischemic stroke; central nervous system tumor, vascular malformation, or vasculitis; and blood dyscrasia or coagulopathy. INR > 3.0 or other nonspecific laboratory abnormalities permitted for diagnosis of possible CAA

for both the classic and modified criteria [6]. In near future, amyloid imaging and CSF markers (see above) should be included to improve diagnostic accuracy without brain biopsy.

7.3 CAA-Related Cognitive Impairment and Neurodegeneration

7.3.1 Dementia Incidence in Non-demented Patients with CAA

Dementia is found in a subgroup of patients with CAA-related ICH at the onset of the initial ICH. In a prospective cohort study, lobar ICH was associated with higher risk of new-onset dementia after spontaneous ICH compared with non-lobar ICH, and disseminated superficial siderosis, cortical atrophy score, a higher number of CMBs, and old age were risk factors of new-onset dementia, which suggest that underlying CAA was a contributing factor [17]. In patients with a CAA-related syndrome including ICH, cognitive symptoms without dementia, CAA-related inflammation, or transient focal neurological symptoms, mild cognitive impairment (MCI) was very prevalent showing lower executive function and processing speed, which was similar to that in vascular cognitive impairment [18]. Cumulated dementia incidence in patients without ICH was estimated to be 14% at 1 year and 73% at 5 years; age, presence of MCI status, medial temporal atrophy, and small vessel disease (SVD) score were independent predictors for dementia conversion in these patients [19]. In a general population of older people, the presence of CMBs located in deep or mixed CMBs, but not lobar CMBs, were associated with a greater cognitive decline of verval memory, processing speed, and executive

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function [20]. Similarly, deep or mixed CMBs, but not purely lobar CMBs, were associated with risk of incident dementia [21]. These results suggest that hypertensive vasculopathy and interaction of hypertensive vasculopathy and CAA, rather than pure CAA-related MBs, may have a definite role in the pathogenesis of cognitive deterioration or dementia incidence.

7.3.2 CAA in Patients with Alzheimer's Disease or Cognitive Impairment

In patients with AD or cognitive impairment, CAA-related lesions are frequently observed. Cerebral MBs were noted in 16.7–32% of AD patients with lobar predominance, which is higher than in the general population (5–6%), when examined by gradient-echo T2∗ MRI, and in 78% of patients with AD dementia or MCI on ultra-high field strength 7T MRI.

In patients with AD or cognitive impairment, the prevalence of cSS is higher than in the general population. In a recent study, cSS was found in 40 of 1504 memory clinic patients (2.7%) with prevalence of 13% for vascular dementia and 5% for AD, including focal cSS in 33 cases and disseminated cSS in 7 cases; the presence of cSS was associated with lobar CMBs, high-degree centrum semiovale perivasuclar spaces, severe white matter hyperintensities, and a higher prevalence of *APOE* ε4/ ε4 genotype compared with those without [22]. MRI-visible perivascular spaces in the centrum semiovale was reported to be independently associated with AD [23]. Thus, cSS as well as CMBs in patients with AD or cognitive impairment indicate the presence of CAA suggesting future risk of CAA-related ICH and CAA-related contributions to cognitive decline.

Besides these MRI markers of CAA, CSF biomarkers were investigated for CAA-related CMBs in AD patients. Our group reported that CAA-related lobar CMBs in AD patients were associated with significantly lower CSF levels of $A\beta_{40}$ and $A\beta_{42}$ compared with those without CMBs, reflecting the deposition of both $A\beta_{40}$ and $A\beta_{42}$ in the cerebrovasculature [24]. CSF $A\beta_{40}$ levels could be a marker of complication of CAA in AD.

For amyloid imaging, current PET ligands such as PiB and florbetapir cannot discriminate vascular from parenchymal deposition or Aβ from other amyloid proteins. It was suggested that early-phase ^{11}C-PiB occipital/posterior cingulate SUVR ratio in CAA patients are significantly lower as compared to AD [25]; however, it is difficult to differentiate AD with CAA from AD without CAA. We need amyloid imaging specific for vascular Aβ deposition for the diagnosis of Aβ-type CAA in AD patients.

7.3.3 Pathological Studies of Dementia and Cognitive Impairment in CAA

Dementia was noted in 74% of individuals with severe CAA at autopsy, including AD, vascular dementia (VaD), mixed dementia of AD and VaD, and vascular variant of AD characterized by severe plaque-like Aβ angiopathy [26]. A prospective cohort study of aging with neuropsychological tests and pathological investigations indicated that moderate-to-very severe CAA is associated with impaired performance in specific cognitive domains, most notably perceptual speed, which is separate from the effect of AD pathology [27]. Further studies with two longitudinal clinical-pathological studies of aging reported that CAA was an independent contributor to AD dementia, over and above AD pathology and other common age-related neuropathologies such as infarcts and Lewy bodies, and CAA was associated with faster rates of decline in global cognition, perceptual speed, episodic memory, and semantic memory, suggesting that CAA pathology independently and importantly contributes to late-life cognitive outcomes [28]. The association of CAA with a lower level of cognition is relatively stable over time in late-life cognitive decline [29]. It is suggested that CAA is a relatively distinct pathological process associated with adverse cognitive outcomes in old age which is independent of AD pathology and other common age-related neuropathologies such as infarcts and Lewy bodies; other mechanisms may be important to link CAA with late-life cognitive outcomes [28].

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7.3.4 CAA-Related Neurodegeneration

CAA-related pathomechanisms other than CAA-related cerebrovascular disorders (hemorrhagic and ischemic lesions) may include CAA-related neurodegeneration. Recent studies suggested CAA-related cortical polionencephalopathy, in addition to leukoencephalopathy (Fig. 7.3).

Our group investigated relationships between CAA-related MBs with cognitive function, gray matter volume, and glucose metabolism in patients with AD using MRI and ^{18}F-FDG PET [30]. The AD patients with CAA-related MBs showed gray matter atrophy in the temporal lobe and cerebellum, and glucose hypometabolism in the temporal lobe, and differences in cognitive profile compared with those without MBs (Fig. 7.4) [30]. Relatively severe leukoaraiosis shown in AD with CAA-related MBs suggested underlying widespread ischemia due to CAA [30]. Preferential involvement (atrophy/hypometabolism) of the temporal lobe in spite of occipital predominance of MBs suggests that the temporal lobe may be susceptible to CAA-induced effects in AD [30].

CAA-related cortical atrophy independent of AD pathology was demonstrated on MRI in patients with hereditary CAA of Dutch type characterized by minimal AD pathology and in patients with sporadic CAA and healthy and AD controls [31]. They also found associations between cortical thickness and vascular dysfunction, measured by BOLD time-to-peak, in patients with hereditary or sporadic CAA; and CAA-related structural lesions, such as lobar MBs or white matter hyperintensity, had no effect on cortical thickness [31]. Incidental cortical MBs in cognitively normal older people are associated with widespread reductions in resting-state CBF assessed by arterial spin labeling of MRI, suggesting the possibility that CAA could result in chronic cerebral hypoperfusion leading to cognitive decline [32]. In addition, reduction of struc-

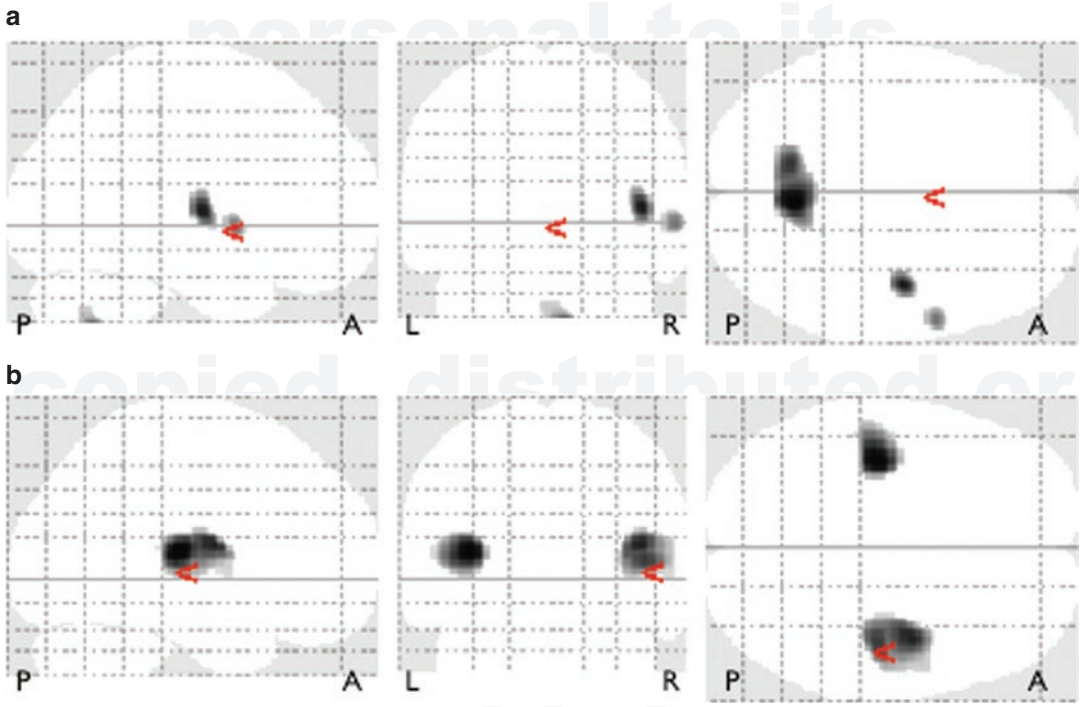

Fig. 7.4 Significantly low gray-matter volume areas (**a**) and significantly reduced ^{18}F-FDG uptake areas (**b**) in the AD patients with CAA-related microbleeds compared with the AD patients without microbleeds. The patients with CAA-related MBs showed gray-matter atrophy in the temporal lobe and cerebellum (**a**), and glucose hypometabolism in the temporal lobe (**b**), compared with those without MBs. See the reference [30] for details. (Height threshold <0.001, uncorrected for multiple comparisons; extent threshold was set to 100 voxels)

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tural brain network efficiency, reconstructed from diffusion tensor imaging, was reported in CAA, which might mediate the relationship between advanced CAA and neurologic dysfunction [33].

7.4 CAA-Related Inflammation and Aβ Immunotherapies for AD and CAA

7.4.1 CAA-Related Inflammation

CAA-related inflammation (CAA-ri) or angiitis is characterized by subacute leukoencephalopathy that is treatable with immunosuppressive therapies [4, 34]. The clinical features include subacute cognitive impairment or behavioral change, focal neurological sign, and seizure, and MRI findings show asymmetric T2 or fluid attenuation inversion recovery (FLAIR) hyperintense white matter lesions, in addition to preexisting CAA-related MBs [4]. Based on clinical and MRI features, diagnostic criteria for CAA-ri was proposed [35]; recently, the modified criteria for CAA-ri have been validated with pathologically confirmed inflammatory or noninflammatory CAA cases, giving a good sensitivity and excellent specificity for the probable criteria [36]. The modified criteria include the followings: (1) clinical symptoms, such as headaches or decrease in consciousness, could occur over longer time frames (i.e., chronic, as well as acute or subacute); (2) WMH patterns would be asymmetric and extend to the immediately subcortical white matter (to meet the more stringent criteria for probable CAA-ri) or simply extend to the immediately subcortical white matter (possible CAA-ri); and (3) the appearance of superficial siderosis would be counted as one bleeding manifestation for CAA [36].

Importantly, CAA-ri is associated with an increase in anti-Aβ antibodies in cerebrospinal fluid (CSF) [15]. Patients with CAA-ri showed cortical amyloid deposition with lower retention in swollen areas as well as an increase of anti-Aβ autoantibodies. Elevated CSF levels of anti-Aβ antibodies as well as positive findings of amyloid PET further specify the diagnosis of CAA-ri, requiring further modification of the criteria for CAA-ri.

It should be noted that cerebrovascular amyloid deposition commonly accompanies immune reactions even in the absence of obvious inflammation [34]. CAA would be associated with an immune mechanism in various degrees for Aβ clearance from the vessel walls. In this sense, "CAA-ri spectrum" would range from very slight inflammation with no or scarce clinical or radiological findings to severe inflammation with clinical and radiological findings typical of CAA-ri/angiitis. Further studies are necessary to explore mildly symptomatic or asymptomatic cases of CAA-ri.

7.4.2 Aβ Immunotherapies for AD and CAA

Clinical as well as experimental studies of Aβ immunotherapies for AD or AD models have reported microvascular abnormalities probably related to CAA. Patients treated with Aβ42 immunization for AD (AN1792, Elan) showed a significantly higher frequency of CAA, cortical microhemorrhages, and microvascular lesions than unimmunized AD controls, suggesting that Aβ immunization resulted in solubilization of Aβ42 in plaques, which migrates out of the brain parenchyma via perivascular interstitial fluid drainage pathways, causing an increase in CAA and CAA-related hemorrhages [37]. While, the longest living had a virtually complete absence of both plaques and CAA [37]. In addition, an AD patient in phase 2a of AN1792 presented with a CAA-related ICH. Meningoencephalitis occurred in 6% of patients treated in the AN1792 trial, and perivascular infiltration of lymphocytes was observed around vessels with CAA.

In a phase 2 trial of bapineuzumab, a humanized monoclonal anti-Aβ antibody, amyloid-related imaging abnormalities (ARIA) were reported: vasogenic edema and sulcal effusions (ARIA-E) in 17%, and microhemorrhages and hemosiderin deposits (ARIA-H) in 47% of the patients with ARIA-E [38]. The findings of ARIA were also reported in other clinical trials of Aβ immunotherapies, including phase 3 trials of bapineuzumab and treatment with gantenerumab. In a phase 1b trial of aducanumab for prodromal or mild AD, ARIA was found

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in 47% of patients treated with 10 mg/kg aducanumab including symptomatic and asymptomatic cases; ARIA included ARIA-E in 41%, ARIA-H in 6%, and both ARIA-E and ARIA-H in 8% [39]. ARIA-E was dose-dependent and more common in *APOE* ε4 carriers [39], as reported in clinical trials with other anti-Aβ antibodies. APOE has a critical role in the removal of plaques and transport of Aβ to the cerebral vasculature induced by Aβ immunotherapy [40]. Thus, Aβ-targeting therapies may result in vascular permeability changes, inflammation, and disruption of CAA-affected vessels. It was recommended by the Alzheimer's Association Research Roundtable Workgroup that the cutoff value of four MBs should be used for exclusion at baseline in trials of amyloid-modifying therapies for AD.

Importantly, vasogenic edema was noted in 2 of 2762 patients with AD at the baseline of the clinical trial as "spontaneous ARIA"; the MRI findings were compatible with those of CAA-ri although they were asymptomatic [41]. CAA-ri is associated with the presence of anti-Aβ autoantibodies in CSF as discussed above [15]. Thus, CAA-ri/angiitis share common pathophysiology with ARIA induced by Aβ immunotherapies. Further studies are required to elucidate immunological mechanisms underlying CAA-ri/angiitis and Aβ immunotherapy-induced ARIA, which would lead to prediction, prevention, and treatment of these disorders.

Currently, no disease-modifying therapies (DMT) are available for CAA. Anti-amyloid therapies for CAA are under development. For Aβ immunotherapies for CAA, ARIA-like CAA-related events should be carefully avoided. Ponezumab is a humanized monoclonal antibody that binds specifically to the carboxyl terminus of $A\beta_{40}$ and showed beneficial effects on reducing CAA and improving vascular reactivity in an animal model [42]. An acceptable safety profile, including ARIA-like events, has been reported for ponezumab in clinical trials for AD. Ponezumab (PF-04360365) was applied to CAA as a phase 2, randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability, pharmacokinetics, and efficacy in adult patients with probable CAA-related hemorrhages (NCT01821118); ponezumab was safe and well-tolerated, but the treatment effect of ponezumab on CAA was opposite to the hypothesized direction [43].

7.5 Transmission of Aβ Pathology and CAA

Many experimental studies have established prion-like transmission of Aβ and other proteins related to neurodegenerative diseases such as tau and α-synuclein; induction of cerebral Aβ deposition in APP transgenic mice has been reported by inoculation with intracerebral injection of brain homogenates from AD patients or AD animal models, through the Aβ-contaminated steel wires, by peripheral (intraperitoneal) inoculation with Aβ-rich brain extracts, and by intracerebral injection of synthetic Aβ peptide (see review [44]). Furthermore, Aβ-type CAA and plaques were induced in primates (marmosets) intracerebrally injected with brain homogenates containing Aβ after very long incubation period.

Human-to-human transmission of Creutzfeldt–Jakob disease (CJD) has occurred through medical procedures resulting in iatrogenic CJD (iCJD). Two major causes of iCJD are (1) peripheral (intramuscular) injection of human cadaveric pituitary-derived growth hormone (hGH) to treat growth hormone deficiency, and (2) grafting of human cadaveric dura mater for neurosurgical procedures. Since 1985, 226 cases of CJD in hGH recipients (until June 2012) have been reported in several countries with the largest numbers of cases occurring in France and the United Kingdom. Dura mater graft-associated iCJD (dCJD) has been found in similar number of cases (n = 228, until June 2012), of which about two-thirds have been reported from Japan (n = 153, until February 2017).

Aβ accumulation in the central nervous system has been reported in both hGH-iCJD and dCJD. Jaunmuktane and his colleagues evaluated eight autopsied patients with hGH-CJD aged 36–51 years, and found that four of them had moderate to severe Aβ pathology in the gray matter and blood vessels (CAA) [45], showing significantly higher severity of CAA and cortical Aβ deposition in hGH-CJD compared with age-matched control patients with prion diseases;

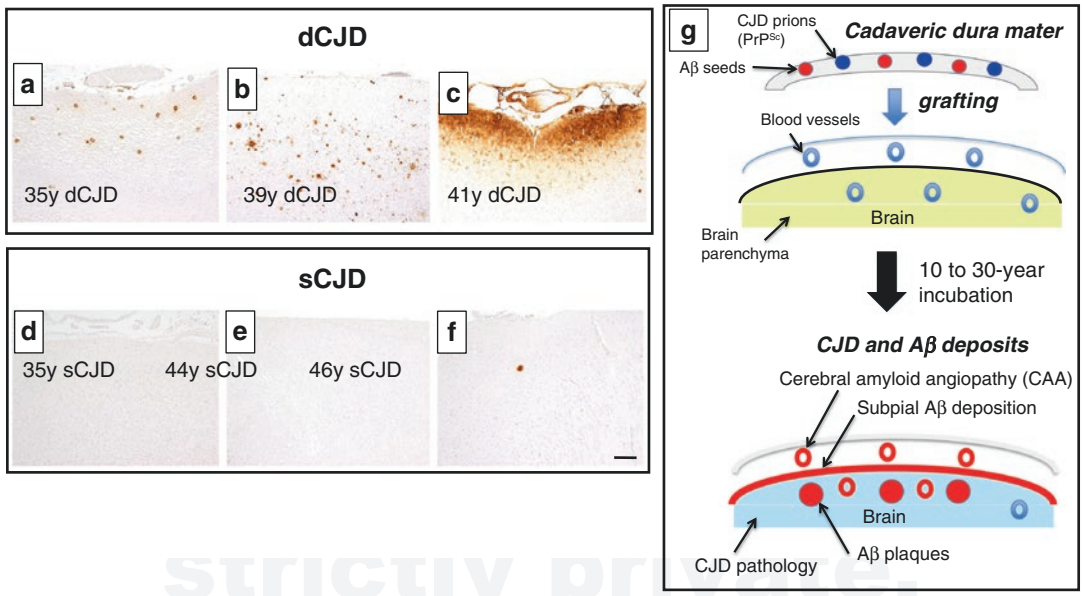

Fig. 7.5 (**a**–**f**) Deposition of Aβ in the brain from patients with dura mater graft-associated CJD (dCJD) (**a**–**c**) and sporadic CJD (**d**–**f**). Immunostaining for Aβ suing anti-Aβ antibody (4G8, monoclonal) in the cerebral cortices of representative cases aged younger than 50 years at autopsy. Parenchymal, subpial, and vascular Aβ deposition is observed in younger dCJD cases (**a**–**c**), while Aβ deposition is scarce in younger sCJD cases (**d**–**f**). Quantitative comparison between dCJD and sCJD with statistical analyses are shown in the reference [47]. Bar = 200 μm. (**g**) A scheme for transmission of Aβ seeds as well as CJD prions via grafting of cadaveric dura mater. Dura mater contaminated with both CJD prions and Aβ seeds was grafted on the brain surface. After 10–30-year incubation, CJD developed with Aβ deposits. Aβ deposition affected more superficial portions of the brain, such as subpial Aβ deposition and meningeal CAA, suggesting direct propagation from the contaminated dura mater

they also reported Aβ deposition in pituitary from patients with high Aβ load in the brain [45]. Furthermore, Ritchie et al. reported Aβ accumulation in 5/12 hGH recipients who died from causes other than CJD, as well as in 18/33 hGH-iCJD patients, indicating that Aβ in the pituitary gland had a seeding effect in the brain of about 50% of all hGH recipients, regardless of whether CJD had developed [46]. Aβ seeding can occur without abnormal prion protein.

Regarding dura mater graft-associated cases, we investigated deposition of Aβ, phosphorylated tau (p-tau), phosphorylated α-synuclein, and phosphorylated transactive response DNA-binding protein of 43 kDa (TDP-43) (p-TDP-43) in 16 Japanese patients with dCJD compared with 21 age-matched patients with sporadic CJD (sCJD) [47]. Subpial Aβ deposition and meningeal CAA in the patients with dCJD were significantly more severe than those in sCJD, and that subpial Aβ deposition and meningeal CAA showed significant positive correlations with incubation period between dura mater graft and death, although there was no significant correlation between the severity of subpial Aβ deposition or meningeal CAA and the age at death or the duration of CJD (Fig. 7.5a–f). The results are consistent with those of our experimental study with intracerebral injection of Aβ seeds to APP transgenic mice at different age, in which the incubation period (the presence of Aβ seeds), but not the age of the host per se, is critical to the initiation and spread of Aβ aggregation in the brain [48]. In addition, there were no differences in p-tau, p-α-synuclein, or p-TDP-43 between dCJD and sCJD cases. Another study with dCJD cases from Europe reported similar results. Importantly, 13% of 84 dura mater samples (age: 79–89 years) from community-based study had Aβ deposition in the form of CAA or amorphous aggregates, indicating that dura mater is a potential source of Aβ seeds [49].

These data suggest that Aβ pathology, including CAA, could be transmitted from humans to humans

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via medical procedures, such as dura mater grafting (Fig. 7.5g) and hGH injection. Importantly, recent reports have described early-onset, non-genetic cases of CAA-related ICH with histories of neurosurgeries in their childhood, suggesting the possibility of transmission of Aβ seeds from contaminated dura mater grafts or surgical instruments leading to clinical onset of CAA-related ICH (see review [50]). Interestingly, intraperitoneal inoculation of Aβ-containing brain extracts to APP transgenic mice resulted in predominantly cerebrovascular amyloid deposition [51]; the peripheral route of Aβ seeding may induce the CAA phenotype, probably related to the transport of Aβ aggregates from the periphery to the brain. Further investigations are necessary to evaluate such events of Aβ seeding and, also, cross-seeding between Aβ and other protein aggregates, as risk for development of CAA as well as AD.

7.6 Future Perspectives

Recent studies have opened novel aspects of CAA in the pathogenesis, pathophysiology, biomarkers, diagnosis, and development of DMT, requiring further studies to understand and overcome CAA. Etiologies of sporadic Aβ-type CAA would be multifactorial, including genetic and nongenetic factors. Age- and AD-related pathomechanisms underlying sporadic Aβ-type CAA need to be further investigated, including disturbance of clearance through periarterial interstitial fluid drainage pathway, possible transmission of CAA-related Aβ seeds, and so on. While, CAA types with single etiologies such as hereditary CAA of Dutch type caused by a point mutation in the APP gene, would be directly linked to pathomechanistic studies and development of DMT for CAA.

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