REVIEW ARTICLE

Biomarkers of Cerebral Amyloid Angiopathy and Neuropathological Relationship with Alzheimer's Disease

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Abstract: Cerebral amyloid angiopathy (CAA), characterized by beta-amyloid (Aβ) deposits within small- to medium-sized blood vessels of the brain and leptomeninges, is known to be associated with an elevated risk of lobar intracerebral hemorrhage. Clinical diagnosis of CAA is complicated due to the limited diagnosis methods and lack of biomarkers for this disease. It was found that CAA has a significantly high probability of comorbidity with Alzheimer's disease (AD) due to the similar neuropathological characteristics known as amyloid-related imaging abnormalities (ARIA). Anti-Aβ monoclonal antibody therapy has been extensively investigated in the treatment of AD patients and applied in several clinical trials worldwide. However, common side effects such as hemorrhage and edema may occur for patients with preclinical or asymptomatic CAA when using antibody therapy. Therefore, it is crucial to identify CAA comorbidity in AD patients before starting anti-Aβ monoclonal antibody therapy. This review summarizes the clinical diagnostic methods and related biomarkers for AD and CAA. Further investigation of CAA for its neuropathological relationship with AD and the discovery of novel biomarkers may pave the way for a more accurate diagnosis and effective prevention of harmful side effects during treatment. It is of great importance to avoid adverse outcomes such as cerebral hemorrhage and edema caused by CAA in the treatment of AD and CAA comorbid patients.

Keywords: Alzheimer's disease; Cerebral amyloid angiopathy; Lecanemab.

INTRODUCTION

Alzheimer's disease (AD) is a common neurodegenerative disease, and one of its pathological manifestations is the deposition of beta-amyloid (Aβ), which can aggravate the degree of dementia in AD patients. Cerebral amyloid angiopathy (CAA) - Aβ depositing in the vessel wall - recognized as a comorbid condition with AD due to the common pathological protein deposition, has garnered growing interest because of its association with an elevated risk of hemorrhage in individuals with AD. There are common pathways in the pathogenesis of CAA and AD, but CAA patients are more likely to have spontaneous cerebral hemorrhage. Therefore, when patients with both AD and CAA receive antibody treatment, prone to cerebral hemorrhage, affecting treatment effectiveness and prognosis. In clinical practice, due to the lack of pathological evidence in most patients and the

limitations of diagnostic criteria based on clinical imaging, including the identification of preclinical CAA and the differentiation of mixed bleeding, it is important to further search for specific diagnostic markers for CAA.

1. ALZHEIMER'S DISEASE

1.1. Pathological Changes in Alzheimer's Disease

AD is a neurodegenerative disease with insidious onset and slow progressive aggravation [1]. The World Report on Alzheimer's Disease 2021 states that there are about 41 million people with AD worldwide. According to the China Alzheimer's Disease Report 2024, there are about 13.1 million AD dementia patients in the elderly aged 60 years and above in China, and the number will increase greatly with the aging of the population, causing a great burden on social and medical resources.

The early symptoms of AD are mild cognitive impairment. With the progression of the disease, cognitive decline, emotional and personality changes, language dysfunction, inability to take care of themselves, and behavioral problems gradually appear. The main pathological features of AD are amyloid plaques formed by Aβ deposition, neurofibrillary tangles formed by abnormal phosphorylation of tau protein, neuronal death, and loss of neural synapses [2]. Recent studies [3] have found that the pathological process of AD is gradually worsening, and these clinical symptoms are the inevitable result of the occurrence and development of the disease. It should be defined by biologic features such as neuropathological changes. Therefore, biomarkers to detect neuropathological changes in AD are particularly important.

1.2. Alzheimer's Disease-Related Biomarkers and Diagnosis

Biomarker classification is the grouping of biomarkers and reflects common protein pathological pathways or pathogenic processes. The new guidelines [3] classify biomarkers into three categories: ① Core biomarkers of AD neuropathologic change (ADNC); ② Nonspecific biomarkers that are important in the pathogenesis of AD but also involved in other brain diseases; ③ Biomarkers of common non-AD comorbidities (Table 1).

Biomarker category	CSF or plasma analytes	Imaging
Core Biomarkers		
Core 1		
A (Aβ proteinopathy)	Aβ 42	Amyloid PET
T1: (phosphorylated and secreted AD tau)	p-tau217, p-tau181, p-tau231	
Core 2		
T2 (AD tau proteinopathy)	MTBR-tau243, other phosphorylated tau forms (e.g., p-tau205), non-phosphorylated mid-region tau fragments	Tau PET
Biomarkers of non-specific processes involved in AD pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MRI, FDG PET
I (inflammation) Astrocytic activation	GFAP	
Biomarkers of non-AD copathology		
Biomarkers of non-AD copathology		Infarction on MRI or CT, WMH
S α-synuclein	αSyn-SAA[a]	

Table 1. Categorization of fluid analyte and imaging biomarkers [3].

Biomarker staging can distinguish the severity of AD biology and divides AD into four biological stages [3]: in stage A, the initial changes in biomarkers; in Stage B, early changes; in stage C, midterm changes; in stage D, late changes (Table 2). Currently, staging by amyloid PET and tau PET or by a combination of T1 fluid labeling and tau PET is clinically feasible.

According to the 2023 NIA-AA diagnostic guidelines, AD is diagnosed based on the following three points: 1. Amyloid PET; 2. Cerebrospinal fluid (CSF) Aβ42/40, CSF p-tau181/Aβ42, CSF t-tau/Aβ42; 3. Plasma markers (There are currently no regulatory approvals for blood biomarkers, although recent studies [4] have found that plasma tests, used alone or in combination with p-tau217 assays, are as accurate as approved CSF assays). According to the degree of cognitive impairment in clinical patients, AD is divided into numerical clinical stages of 0-6 stages to accurately assess the patient's condition and formulate corresponding treatment plans.

(See Table 1)

Notes: P-tau231, p-tau205, MTBR-tau243, and non-phosphorylated tau fragments are included in this table because they are discussed in the text; however, these analytes have not undergone the same level of validation testing as other core biomarkers. Biomarkers are categorized based on four criteria. First, three broad mechanistic groupings have been identified. Second, biomarkers are subclassified based on the proteinopathy or pathophysiologic pathway that each measure (e.g., A, T1, T2, N, etc.). Third, within the core category, we distinguish between Core 1 and Core 2 biomarkers. Fourth, imaging and fluid analyte biomarkers are listed separately within each category.

Abbreviations: Aβ amyloid beta, AD Alzheimer's disease, αSyn-SAA alphasynuclein seed amplification assay, CSF cerebrospinal fluid, CT computed tomography, FDG fluorodeoxyglucose, GFAP glial fibrillary acidic protein, MRI magnetic resonance imaging, MTBR microtubule-binding region, NfL neurofilament light chain, PET positron emission tomography, WMH white matter hyperintensity.

A fluid analyte that is presently informative only when measured in CSF. No notation is used if the fluid analyte is informative with plasma or CSF.

	Initial-stage biomarkers (A)	Early-stage biomarkers (B)	Intermediate-stage biomarkers (C)	Advanced-stage biomarkers (D)
Fluid staging	CSFAβ42/40, ptau181/Aβ42, t-tau/Aβ42, and accurate plasma assay	Other p-tau forms (e.g., p-tau205)	MTBR-tau243	Non-phosphorylated tau fragments

Table 2. Conceptual biological staging with fluid biomarkers [3].

Notes: Staging may be accomplished by (1) a combination of amyloid PET and tau PET or (2) a combination of Core 1 fluid biomarkers (which would establish biological stage A or higher) plus tau PET (which would be used to discriminate between stages). The approach to determining A+ versus A− with amyloid PET may need special consideration in autosomal dominant Alzheimer's disease (ADAD) and Down syndrome AD (DSAD).

Abbreviations: Aβ amyloid beta, CSF cerebrospinal fluid, PET positron emission tomography, p-tau phosphorylated tau.

2. CEREBRAL AMYLOID ANGIOPATHY

2.1. Pathological Changes in Cerebral Amyloid Angiopathy

CAA is a type of age-related cerebral small vessel disease caused by Aβ protein deposition in the tunica media and adventitia of small vessels in the cerebral cortex and leptomeninges. The destruction of vessel wall integrity secondary to Aβ protein deposition can lead to clinically recurrent lobar hemorrhage and age-related cognitive dysfunction [5]. Pathologically, CAA can be divided into two types:

in type I, Aβ was mainly deposited in cortical capillaries, which was closely related to Aβ deposition in AD; in type II CAA, Aβ was found in the leptomeninges, cortical arteries and arterioles (Fig. 1). There is a common pathway in the pathogenesis and a high comorbidity rate between CAA and AD [6], but the relationship and difference between the two have not been fully clarified.

A systematic review of clinical and pathological studies showed that the prevalence of CAA was 20%-40% in the non-dementia population, while it was as high as 50%-60% in the dementia population [7]. Based on the pathological data of the National Human Brain Bank for Development and Function, it is found that patients with CAA and AD comorbid with cognitive impairment are usually more common. Among 483 donors with a mean age of 78.8 years, 31.3% had CAA pathology. Among them, 64.9% of CAA patients also had AD, and 55.7% of AD patients were CAA positive (unpublished data). A study [8] found that among 87 white subjects (69 cases of CAA and 18 cases of NC), more than 62% (n=42) of CAA patients showed cognitive impairment. In addition, in AD and CAA patients, apolipoprotein E (ApoE) allele changes are observed simultaneously, and ApoE gene affects Aβ clearance or accumulation.

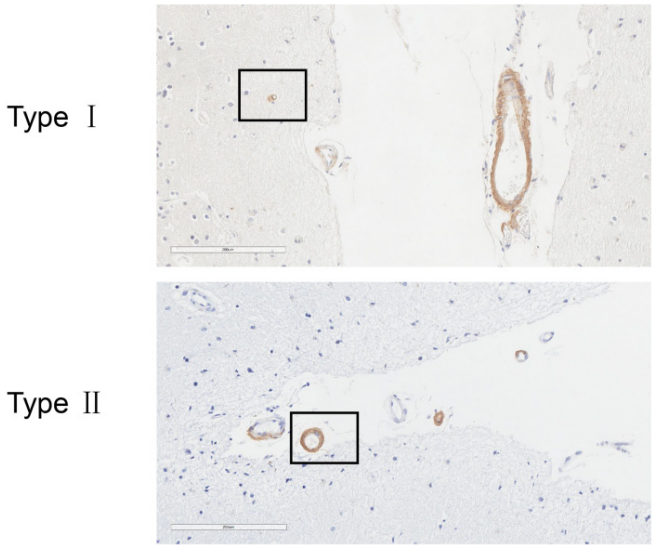

Figure 1. CAA-positive vessels.

Anti-amyloid-β immunostaining (left, mouse monoclonal antibody, diluted 1:500, DAKO Cat#M0872) of a postmortem section of the occipital lobe from a 95-year-old male donor and a 74-year-old female donor in the National Human Brain Bank for Development and Function reveals existing Aβ plaques in cortical vessels.

2.2. Diagnosis of Cerebral Amyloid Angiopathy

According to the newly revised Boston criteria (Table 3) [9], no clinical means have been found to confirm CAA, and the established CAA diagnosis can only be established by full autopsy certificate with severe vascular lesions. According to the anatomical distribution of CAA-positive vessels, the severity of CAA was divided into grade III: in Grade I, CAA was limited to leptomeningeal or parenchymal vessels in the neocortex (frontal, parietal, temporal, and occipital cortex). In grade II, involvement extends to vessels in the allogeneic cortex (cingulate, entorhinal cortex, and hippocampus), cerebellum, and midbrain. Grade III includes all regions of grade II, as well as the lower brainstem, basal ganglia and thalamus [10]. The severity of individual vessels is also graded: 0(normal)=no CAA; 1(mild)=Aβ-deposits in the vessel wall without loss of smooth muscle cells in the vessel wall; 2(moderate)=Aβ-deposits in the vessel wall accompanied by degeneration of the smooth muscle cell layer; and 3(severe)=extensive Aβ-deposition and focal vessel wall fragmentations, microaneurysms, signs of hemorrhage, and fibrinoid necrosis [11].

As a cerebrovascular pathological phenomenon, CAA can cause a variety of clinical manifestations

or no symptoms. Some studies have proposedthat many elderly patients have no obvious clinical symptoms, which makes CAA diagnosis more difficult, and it cannot be completely diagnosed by only the existing clinical-imaging examination [12]. On the other hand, due to the hyalinization of CAA vessels, if there is a need for surgical intervention but no CAA is diagnosed, the occult patients with vascular rupture and bleeding during surgery will be extremely difficult to rescue, and the mortality rate is exceptionally high. Therefore, it is critically important to find CAA biomarkers for CAA screening, diagnosis, staging, disease progression prediction and clinical trials in clinical practice.

2.3. Brain Injury of Cerebral Amyloid Angiopathy and Alzheimer's Disease

Advanced CAA is associated with cognitive impairment. The pathogenesis of cognitive impairment in CAA is likely multifactorial, involving contributions from both vascular injury and AD pathology. CAA frequently coexists with AD, appearing in moderate to severe forms in 30 of 117 (26%) AD brains in an autopsy series; CAA with hemorrhage was observed in six (5.1%) of these cases [13,14]. Another autopsy study revealed that patients with both CAA and AD exhibited more severe cognitive impairment than those with AD alone [15]. Similarly, an MRI study in AD patients demonstrated that the presence of multiple microbleeds was associated with worse cognitive performance [16]. However, only about 25% of CAA patients appear to have clinical histories of dementia before their first hemorrhage [17].

CAA is characterized by vascular amyloid deposits that are biochemically similar to the material found in senile plaques in AD. Some cases of early-onset CAA are caused by variant forms of the gene encoding APP and are inherited in an autosomal dominant pattern. While most of these variants are also associated with at least some of the neuropathologic features of AD, at least two APP variants (Glu693Gln and Leu705Val) have been reported to cause autosomal-dominant CAA with minimal parenchymal amyloid plaques or neurofibrillary tangles [18-20]. The Dutch-type Glu693Gln APP pathologic variant is associated with cerebral amyloid deposition and tends to follow a more aggressive course than that seen in patients with sporadic CAA [21]. Additionally, patients carrying the ApoE epsilon 2 (ε2) or epsilon 4 (ε4) alleles appear to be at a greater risk for CAA-related hemorrhage compared to those with only the common ApoE epsilon 3 (ε3) allele [22-26]. One systematic review found a dose-dependent association between ApoE ε4 and sporadic CAA [27]. ApoE ε4 has been shown to promote the deposition of Aβ-peptide in AD [28] as well as following severe head injury [29]. The ApoE ε2 and ε4 alleles act through distinct mechanisms. While ApoE ε4 increases Aβ-peptide deposition [28], ApoE ε2 causes amyloid-laden vessels to undergo changes such as concentric wall splitting and necrosis, which predispose them to rupture [23,30,31]. Patients with CAA who carry both ApoE ε2 and ε4 alleles appear to experience particularly early disease onset and a higher risk of early recurrence [23,32]. Additionally, carriers of the ApoE ε2 allele tend to have larger intracerebral haemorrhage (ICH) volumes, increased mortality, and worse functional outcomes compared to non-carriers, while these associations are not observed for carriers of the ApoE ε4 allele [33].

Cerebrovascular disease has been linked to worse cognitive performance in patients with AD. Clinicopathologic studies suggest that cerebrovascular disease lowers the threshold for clinical dementia in patients with a neuropathologic diagnosis of AD [34-44]. Decreased blood flow before Aβ deposition has been observed in both mouse models of AD and human studies. This reduction in blood flow has been proposed to contribute directly to amyloid accumulation, likely by impairing the clearance of amyloid. Additionally, vascular factors may contribute to the breakdown of the blood-brain barrier [45]. Numerous studies have identified an increased risk of AD in association with various neuroimaging or pathologic markers of cerebrovascular disease, including atherosclerosis in the circle of Willis [46-49], periventricular white matter lesions [41,50-52], cerebral microbleeds [53], and cortical infarcts [41,42,54]. Based on these and other findings, some researchers conclude that a vascular mechanism may be a primary etiologic factor in AD [55].

2.4. Cerebral Amyloid Angiopathy related biomarkers

2.4.1. Brain Imaging Markers

The main imaging feature of CAA is lobar cerebral hemorrhage. Other MRI biomarkers include strict lobar microbleeds, superficial cortical

siderosis, multiple subcortical spots WMH, severe perivascular spaces in the centrum semiovale, and cortical microinfarcts [56]. Multiple lobar microbleeds detected on T2*/susceptibility weighted imaging (SWI) MRI are considered to be one of the signature biomarkers for the presence of CAA. The key features of hemorrhagic neuroimaging of CAA are acute or chronic hemorrhages of cortical sulci and adjacent sulci (manifested as superficial cortical siderosis in chronic cases and sulci subarachnoid hemorrhage in acute cases). This may indicate repeated leakage of blood from CAA-positive vessels into the subarachnoid space. Siderosis or cSAH is perhaps the most clinically relevant manifestations of the disease: ① It is the trigger of transient focal neurological symptoms ("amyloid symptoms") [57, 58]; ② It has been shown to have a high risk of symptomatic lobar cerebral hemorrhage, which is critically important for CAA clinical nursing [59-61]; ③ It may be an independent risk factor for new-onset dementia after cerebral hemorrhage [62]. Notably, these effects of siderosis or cSAH were independent of concurrent microbleeds and were higher than the effects of any microbleeds. The critical role of cortical superficial siderosis in CAA neurological dysfunction may be related to the neuropathological observations between the leptomeningeal cortical layers [63].

Additionally, CAA is one of the main causes of amyloid-related imaging abnormalities (ARIA), especially in elderly patients [64], and the pathological changes of CAA mostly appear in the form of microbleeds. ARIA specifically refers to a series of imaging manifestations of magnetic resonance imaging abnormalities, including cerebral hemorrhage (hemorrhage type, ARIA-H) and cerebral edema (effusion type, ARIA-E). The occurrence of ARIA is closely related to ApoE4/4 [65], which are more prominent when combined with CAA [66,67]. CAA-related intracerebral hemorrhage or microbleeds are located in the superficial brain lobe and tend to involve the posterior temporal lobe and occipital lobe, consistent with the selective location of Aβ deposition in CAA [68]. In patients with a large number of cerebral microbleeds, the lesions tend to accumulate in the same brain lobe [56]. Different from hypertensive intracerebral hemorrhage (which mainly involves deep gray matter and brain stem), lobar hemorrhage and microhemorrhage are also the main clues for antemorporeal diagnosis of CAA [68].

2.4.2. PET Testing

Positron Emission Computed Tomography (PET) is an advanced clinical imaging technique in the field of nuclear medicine, which plays an important role in the diagnosis of brain diseases. ^{11}C-Pittursburgh Complex B (PiB) is a commonly used marker because it can bind to Aβ in blood vessels and brain parenchyma as derivatives of Aβ staining agent thioflavin Tand thus be taken up by PET [68, 69, 70]. In addition, three other ^{18}F labeled imaging agents, florbetaben [71] (AV-1), florbetapir [72] (AV-45), and flutemetamol [73] (GE-067), have been approved for clinical imaging of Aβ PET. PiB uptake was increased in CAA patients compared with age-matched healthy controls [74]. For the qualitative evaluation of PiB, the positive rate of CAA patients can reach 77%-92%, and negative PiB can basically rule out CAA, but the specificity of PiB positive for CAA is relatively low, because it cannot identify Aβ deposition in blood vessels and brain parenchyma, and cannot determine the source of Aβ [75].

Therefore, it is very difficult to differentiate CAA from AD by quantitative or qualitative evaluation of PET uptake. There were differences in the preferential deposition sites of Aβ between CAA and AD patients (in CAA, Aβ is preferentially accumulated in the occipital lobe; in AD, the frontal lobe lesions are prominent and usually do not involve the occipital lobe). Therefore, the difference of PiB uptake in different regions has been highly expected in the differentiation of CAA and AD, but the results of the two groups of individuals overlap. In addition, cases with high uptake in the frontal lobe and low uptake in the occipital lobe were finally diagnosed as CAA by pathology [76,77]. Moreover, the ApoE ε4 allele or ApoE ε4 genotype increases the risk of Aβ PET imaging positivity in patients [78]. In conclusion, although the sensitivity is high, the specificity is not high, and the ratio of PET uptake in occipital lobe to whole cortex cannot accurately distinguish CAA from AD.

In recent years, tau PET has also received widespread attention. Flortaucipil is a radioactive tracer that binds to tau protein. It can detect tau accumulation and its distribution in the brain to accurately evaluate its role in clinical manifestations of diseases. A study published in 2023 found that Tau PET can better predict cognitive decline in patients [79]. There is a significant correlation between microbleeds and Aβ pathology and tau accumulation in CAA individuals without cognitive impairment.

It was found that in the presence of Aβ pathology, cerebrovascular pathology altered the accumulation of tau in the early stages of AD; that is, the co-occurrence of microbleeds and amyloid beta pathology was related to the larger accumulation of tau aggregates in the early stages of the disease. It opens the possibility that interventions targeting microbleeds may reduce the accumulation rate of tau protein [80]. It is meaningful to incorporate tau PET into routine clinical evaluation as it can assess individual prognosis and select the most appropriate treatment strategy for each patient.

2.4.3. Cerebral Amyloid Angiopathy-Related Testing

Studies have found that Aβ levels in the cerebrospinal fluid of CAA patients are abnormally changed. The level of Aβ40 and Aβ42 in sporadic CAA patients was lower than that in healthy controls [81]. Besides, the levels of Aβ40 and Aβ42 in cerebrospinal fluid of patients with symptomatic and presymptomatic Dutch type hereditary CAA were also lower than those of healthy controls [82]. At present, the existing clinical diagnostic methods are not enough to determine the occurrence of CAA, and the use of biomarkers to identify CAA is a convenient way for clinical diagnosis. However, there are still great challenges in developing molecular markers for CAA diagnosis, and more attention should be paid to the development of CAA diagnostic markers. In addition, proteomic results have shown that SEMA3G and HTRA1 have the potential to become molecular diagnostic markers for CAA, as they are highly expressed in CAA blood vessels [65,83].

	Boston Criteria (Version 2.0)
1.Definite CAA	Full post-mortem examination demonstrating: Presentation with spontaneous ICH, TFNEs, cSAH, or CI/Dementia; Severe CAA with vasculopathy; Absence of other diagnostic lesion.
2.Probable CAA with supporting pathology	Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating: Presentation with spontaneous ICH, TFNEs, cSAH, or CI/Dementia; Some degree of CAA in specimen; Absence of other diagnostic lesion.
3.Probable CAA	Clinical data and MRI demonstrating: Age≥50 years; Presentation with spontaneous ICH, TFNEs, or CI/Dementi; ≥2 of the following strictly lobar haemorrhagic lesions on T2*-weighted MRI, in any combination: ICH, CMB, cSS/cSAH foci; ***OR*** I lobar haemorrhagic lesion + I white matter feature (Severe CSO-PVS or WMH-MS); Absence of any deep haemorrhagic lesions (ICH, CMB) on T2*weighted -MRI; Absence of other cause of haemorrhagic lesions*; Haemorrhagic lesion in cerebellum not counted as either lobar or deep haemorrhagic lesion.
4.Possible CAA	Clinical data and MRI demonstrating: Age≥50 years; Presentation with spontaneous ICH, TFNEs, or CI/Dementia; Absence of other cause of haemorrhage*; I strictly lobar haemorrhagic lesion on T2*-weighted MRI: ICH, CMB, cSS/cSAH focus; ***OR*** I white matter feature (Severe CSO-PVS or WMH-MS); Absence of any deep haemorrhagic lesions (ICH, CMB) on T2*-weighted MRI; Absence of other cause of haemorrhagic lesions*; Haemorrhagic lesion in cerebellum not counted as either lobar or deep haemorrhagic lesion.

Table 3. Boston criteria version 2.0 for sporadic CAA [9].

* Other causes of haemorrhagic lesion: antecedent head trauma, haemorrhagic transformation of an ischemic stroke, arteriovenous malformation, haemorrhagic tumor, central nervous system vasculitis.

Abbreviations: CAA cerebral amyloid angiopathy, MRI magnetic resonance imaging, ICH intracerebral haemorrhage, TFNE transient focal neurologic episodes, CI cognitive impairment, CMB cerebral microbleed, cSS cortical superficial siderosis, cSAH convexity subarachnoid haemorrhage, CSO-PVS visible perivascular spaces in the centrum semiovale, WMH-MS white matter hyperintensities in a multispot pattern

3. MONOCLONAL ANTIBODY THERAPY DRUGS FOR ALZHEIMER'S DISEASE AND POOR PROGNOSIS OF CEREBRAL AMYLOID ANGIOPATHY

The pathogenesis of AD is not completely clear, and related hypotheses include the Aβ cascade hypothesis, tau protein hyperphosphorylation hypothesis, the interaction between Aβ and cerebrovascular abnormalities, neuroinflammation hypothesis and oxidative stress hypothesis, etc. Among them, the Aβ cascade hypothesis has been in a relatively important position in drug development [84-87]. Traditional drugs for the treatment of AD are mainly based on drug treatment for stages that have shown typical dementia symptoms, including cholinesterase inhibitors and glutamate receptor antagonists, but the overall efficacy still needs to be further improved. Research has found that AD patients receiving high doses (10 mg/kg) of Aducanumab have an incidence of 41.3% for ARIA and 35.2% for ARIA-E [88]; The incidence of ARIA in AD patients receiving Donanemab (first 3 doses of 700 mg, sequential treatment of 1400 mg) reached 36.8% [89]; For AD patients receiving Solanezumab (400 mg), although the incidence of ARIA is relatively low, with ARIA-E and ARIA-H at 0.9% and 4.9%, respectively, it does not alleviate the cognitive decline of patients [90].

Lecanemab is the first AD drug in the world to receive full approval from the U.S. Food and Drug Administration (FDA) in nearly 20 years. It is a single-gram, anti-Aβ antibody that acts by highly specific binding to Aβ fibrils to eliminate toxic, soluble Aβ aggregates, thereby improving cognitive function and quality of life. Clinical trial data [91] have shown that Lecanemab treatment has a significantly poor prognosis, that is, cerebral edema and cerebral hemorrhage. Studies have found that the main risk factors for cerebral edema are the antibody dose and the presence of the ApoE4 allele [91]. The mechanism of cerebral edema has not been elucidated, but it may be due to the direct binding of Aβ antibodies to Aβ deposits [92-94]. A recent study [95] found that a patient who received three doses of intravenous lecanemab developed acute cerebral hemorrhage after treatment of acute ischemic stroke syndrome. The autopsy results showed that the patient had multifocal parenchymal hemorrhage, CAA and AD neuropathological changes, and diffuse vasculitis with necrotizing angiopathy. These studies suggest that CAA may be responsible for the poor outcomes such as ICH and cerebral edema in AD patients treated with Lecanemab.

When monoclonal antibody drugs are used to treat AD patients, patients with CAA comorbidity are more likely to have the risk of cerebral edema and cerebral hemorrhage, which provides new ideas for the possible mechanism of the poor prognosis of drugs. More importantly, the diagnosis and related pathological changes of CAA - especially asymptomatic CAA, should be paid attention to because it is closely related to the treatment and prognosis of patients.

4. CONCLUSION AND FUTURE WORK

In conclusion, we summarized the clinical diagnostic methods and related biomarkers for AD and CAA patients and discussed the adverse prognosis associated with CAA when using monoclonal antibody drugs to treat AD patients in clinical treatment. These results suggest that there may be a large number of asymptomatic CAA patients in clinical practice. Although the diagnosis and treatment of CAA have been paid more and more attention, the pathogenic mechanism of CAA is still uncertain, and the existing clinical diagnostic methods cannot confirm CAA. Therefore, the discovery of specific markers of CAA is critically important for the early diagnosis and late treatment of the disease. In the future, it will possibly use omics research to seek CAA relative molecular markers and the common targets of CAA and AD and explore the relevant pathogenic mechanisms to clinically diagnose CAA. And when treating patients with CAA and AD comorbidities, it can adverse outcomes such as cerebral hemorrhage and edema caused by CAA can be avoided, and the survival rate of patients.

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Author contributions

T.J. drafted the manuscript, X.Y. and Y.S. helped with partial literature search and summary, W.Q. and J.N. revised the manuscript, X.Q. supervised and finalized the manuscript.

Conflict of Interest Disclosures

The authors declare no competing interests.

List of Abbreviations

CAA – cerebral amyloid angiopathy
AD – Alzheimer's disease
ARIA – Amyloid-related imaging abnormalities
Aβ – β-amyloid
ADNC – Alzheimer's disease neuropathologic change
PET – positron emission computed tomography
CSF – cerebrospinal fluid
αSyn-SAA – alphasynuclein seed amplification assay
CT – computed tomography
FDG – fluorodeoxyglucose
GFAP – glial fibrillary acidic protein
MRI – magnetic resonance imaging
MTBR – microtubule-binding region
NfL – neurofilament light chain
WMH – white matter hyperintensity
p-tau – phosphorylated tau
ApoE – apolipoprotein E
ARIA-H – Amyloid-related imaging abnormalities hemorrhage type
ARIA-E – Amyloid-related imaging abnormalities effusion type
SWI – susceptibility weighted imaging
PiB – 11C-Pittursburgh complex B
AV-1 – florbetaben
AV-45 – florbetapir
GE-067 – flutemetamol
SEMA3G – Semaphorin 3G
HTRA1 – high-temperature requirement A1
ICH – intracerebral haemorrhage
TFNE – transient focal neurologic episodes
CI – cognitive impairment
CMB – cerebral microbleed
cSS – cortical superficial siderosis
cSAH – convexity subarachnoid haemorrhage
CSO-PVS – visible perivascular spaces in the centrum semiovale
WMH-MS – white matter hyperintensities in a multispot pattern
FDA – Food and Drug Administration ♦

REFERENCES

1. M Canevelli, N Vanacore, *et al*. Overtreating Alzheimer's Disease. J Prev Alzheimers Dis. 2021;8(2):234-236.
2. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics.Science.2002 Jul 19;297(5580):353-6.
3. Clifford R Jack Jr, J Scott Andrews, *et al*. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimers Dement. 2024 Aug;20(8):5143-5169.
4. Joseph Therriault, Nicholas James Ashton, *et al*. Comparison of two plasma p-tau217 assays to detect and monitor Alzheimer's pathology. EBioMedicine. 2024 Apr:102:105046.
5. Bales KR, O'Neill SM, Pozdnyakov N, Pan F, Caouette D, Pi Y, *et al*. Passive immunotherapy targeting amyloid-beta reduces cerebral amyloid angiopathy and improves vascular reactivity. Brain 2016; 139(Pt 2): 563-77.
6. Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, *et al*. Cerebral amyloid angiopathy and Alzheimer disease-one peptide, two pathways. Nat Rev Neurol, 2020, 16(1):30-42.
7. Keage HA, Carare RO, Friedland RP, *et al*. Population studies of sporadic cerebral amyloid angiopathy and dementia: a systematic review. BMC Neurol, 2009, 9: 3.
8. Marc Dörner, Anthony Tyndall, Neuropsychiatric symptoms and lifelong mental activities in cerebral amyloid angiopathy - a cross-sectional study. Alzheimers Res Ther. 2024 Sep 4;16(1):196.

9. Andreas Charidimou, Gregoire Boulouis, *et al*. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. Lancet Neurol. 2022 Aug;21(8):714-725.
10. Thal DR, Ghebremedhin E, Orantes M, Wiestler OD. Vascular pathology in Alzheimer disease: correlation of cerebral amyloid angiopathy and arteriosclerosis/lipohyalinosis with cognitive decline. Journal of Neuropathology and Experimental Neurology. 2003;62:1287-301.
11. Dietmar Rudolf Thal, W Sue T Griffin, *et al*. Cerebral amyloid angiopathy and its relationship to Alzheimer's disease. Acta Neuropathol. 2008 Jun;115(6):599-609.
12. Aaron P Schultz, Reina W Kloet, *et al*. Amyloid imaging of dutch-type hereditary cerebral amyloid angiopathy carriers. Ann Neurol. 2019 Oct;86(4):616-625.
13. Arvanitakis Z, Leurgans SE, Wang Z, *et al*. Cerebral amyloid angiopathy pathology and cognitive domains in older persons. Ann Neurol 2011; 69:320.
14. Ellis RJ, Olichney JM, Thal LJ, *et al*. Cerebral amyloid angiopathy in the brains of patients with Alzheimer's disease: the CERAD experience, Part XV. Neurology 1996; 46:1592.
15. Pfeifer LA, White LR, Ross GW, *et al*. Cerebral amyloid angiopathy and cognitive function: the HAAS autopsy study. Neurology 2002; 58:1629.
16. Goos JD, Kester MI, Barkhof F, *et al*. Patients with Alzheimer disease with multiple microbleeds: relation with cerebrospinal fluid biomarkers and cognition. Stroke 2009; 40:3455.
17. Greenberg SM, Briggs ME, Hyman BT, *et al*. Apolipoprotein E epsilon 4 is associated with the presence and earlier onset of hemorrhage in cerebral amyloid angiopathy. Stroke 1996; 27:1333.
18. Obici L, Demarchi A, de Rosa G, *et al*. A novel AbetaPP mutation exclusively associated with cerebral amyloid angiopathy. Ann Neurol 2005; 58:639.
19. Kozberg MG, van Veluw SJ, Frosch MP, Greenberg SM. Hereditary cerebral amyloid angiopathy, Piedmont-type mutation. Neurol Genet 2020; 6:e411.
20. Maat-Schieman ML, Radder CM, van Duinen SG, *et al*. Hereditary cerebral hemorrhage with amyloidosis (Dutch): a model for congophilic plaque formation without neurofibrillary pathology. Acta Neuropathol 1994; 88:371.
21. van Etten ES, Gurol ME, van der Grond J, *et al*. Recurrent hemorrhage risk and mortality in hereditary and sporadic cerebral amyloid angiopathy. Neurology 2016; 87:1482.
22. Nicoll JA, Burnett C, Love S, *et al*. High frequency of apolipoprotein E epsilon 2 allele in hemorrhage due to cerebral amyloid angiopathy. Ann Neurol 1997; 41:716.
23. Greenberg SM, Vonsattel JP, Segal AZ, *et al*. Association of apolipoprotein E epsilon2 and vasculopathy in cerebral amyloid angiopathy. Neurology 1998; 50:961.
24. Greenberg SM, Rebeck GW, Vonsattel JP, *et al*. Apolipoprotein E epsilon 4 and cerebral hemorrhage associated with amyloid angiopathy. Ann Neurol 1995; 38:254.
25. Biffi A, Sonni A, Anderson CD, *et al*. Variants at APOE influence risk of deep and lobar intracerebral hemorrhage. Ann Neurol 2010; 68:934.
26. Maxwell SS, Jackson CA, Paternoster L, *et al*. Genetic associations with brain microbleeds: Systematic review and meta-analyses. Neurology 2011; 77:158.
27. Rannikmäe K, Samarasekera N, Martînez-Gonzâlez NA, *et al*. Genetics of cerebral amyloid angiopathy: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2013; 84:901.
28. Schmechel DE, Saunders AM, Strittmatter WJ, *et al*. Increased amyloid beta-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer disease. Proc Natl Acad Sci U S A 1993; 90:9649.
29. Nicoll JA, Roberts GW, Graham DI. Apolipoprotein E epsilon 4 allele is associated with deposition of amyloid beta-protein following head injury. Nat Med 1995; 1:135.
30. McCarron MO, Nicoll JA, Ironside JW, *et al*. Cerebral amyloid angiopathy-related hemorrhage. Interaction of APOE epsilon2 with putative clinical risk factors. Stroke 1999; 30:1643.
31. McCarron MO, Nicoll JA, Stewart J, *et al*. The apolipoprotein E epsilon2 allele and the pathological features in cerebral amyloid angiopathy-related hemorrhage. J Neuropathol Exp Neurol 1999; 58:711.
32. O'Donnell HC, Rosand J, Knudsen KA, *et al*. Apolipoprotein E genotype and the risk of recurrent lobar intracerebral hemorrhage. N Engl J Med 2000; 342:240.

33. Biffi A, Anderson CD, Jagiella JM, *et al*. APOE genotype and extent of bleeding and outcome in lobar intracerebral haemorrhage: a genetic association study. Lancet Neurol 2011; 10:702.
34. Vemuri P, Lesnick TG, Przybelski SA, *et al*. Vascular and amyloid pathologies are independent predictors of cognitive decline in normal elderly. Brain 2015; 138:761.
35. Chui HC, Zarow C, Mack WJ, *et al*. Cognitive impact of subcortical vascular and Alzheimer's disease pathology. Ann Neurol 2006; 60:677.
36. Snowdon DA, Greiner LH, Mortimer JA, *et al*. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA 1997; 277:813.
37. Bennett DA, Wilson RS, Arvanitakis Z, *et al*. Selected findings from the Religious Orders Study and Rush Memory and Aging Project. J Alzheimers Dis 2013; 33 Suppl 1:S397.
38. Toledo JB, Arnold SE, Raible K, *et al*. Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. Brain 2013; 136:2697.
39. Troncoso JC, Zonderman AB, Resnick SM, *et al*. Effect of infarcts on dementia in the Baltimore longitudinal study of aging. Ann Neurol 2008; 64:168.
40. Riekse RG, Leverenz JB, McCormick W, *et al*. Effect of vascular lesions on cognition in Alzheimer's disease: a community-based study. J Am Geriatr Soc 2004; 52:1442.
41. Kövari E, Gold G, Herrmann FR, *et al*. Cortical microinfarcts and demyelination affect cognition in cases at high risk for dementia. Neurology 2007; 68:927.
42. Schneider JA, Boyle PA, Arvanitakis Z, *et al*. Subcortical infarcts, Alzheimer's disease pathology, and memory function in older persons. Ann Neurol 2007; 62:59.
43. Brickman AM, Honig LS, Scarmeas N, *et al*. Measuring cerebral atrophy and white matter hyperintensity burden to predict the rate of cognitive decline in Alzheimer disease. Arch Neurol 2008; 65:1202.
44. Xie S, Xiao JX, Gong GL, *et al*. Voxel-based detection of white matter abnormalities in mild Alzheimer disease. Neurology 2006; 66:1845.
45. Ighodaro ET, Abner EL, Fardo DW, *et al*. Risk factors and global cognitive status related to brain arteriolosclerosis in elderly individuals. J Cereb Blood Flow Metab 2017; 37:201.
46. Roher AE, Esh C, Rahman A, *et al*. Atherosclerosis of cerebral arteries in Alzheimer disease. Stroke 2004; 35:2623.
47. Honig LS, Kukull W, Mayeux R. Atherosclerosis and AD: analysis of data from the US National Alzheimer's Coordinating Center. Neurology 2005; 64:494.
48. Yarchoan M, Xie SX, Kling MA, *et al*. Cerebrovascular atherosclerosis correlates with Alzheimer pathology in neurodegenerative dementias. Brain 2012; 135:3749.
49. Dolan H, Crain B, Troncoso J, *et al*. Atherosclerosis, dementia, and Alzheimer disease in the Baltimore Longitudinal Study of Aging cohort. Ann Neurol 2010; 68:231.
50. de Leeuw FE, Korf E, Barkhof F, Scheltens P. White matter lesions are associated with progression of medial temporal lobe atrophy in Alzheimer disease. Stroke 2006; 37:2248.
51. Behl P, Bocti C, Swartz RH, *et al*. Strategic subcortical hyperintensities in cholinergic pathways and executive function decline in treated Alzheimer patients. Arch Neurol 2007; 64:266.
52. Knopman DS, Griswold ME, Lirette ST, *et al*. Vascular imaging abnormalities and cognition: mediation by cortical volume in nondemented individuals: atherosclerosis risk in communities-neurocognitive study. Stroke 2015; 46:433.
53. Akoudad S, Wolters FJ, Viswanathan A, *et al*. Association of Cerebral Microbleeds With Cognitive Decline and Dementia. JAMA Neurol 2016; 73:934.
54. Schneider JA, Wilson RS, Bienias JL, *et al*. Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology. Neurology 2004; 62:1148.
55. de la Torre JC. Alzheimer disease as a vascular disorder: nosological evidence. Stroke 2002; 33:1152.
56. RosandJ, MuzikanskyA, *et al*. Spatial clustering of hemorrhages in probable cerebral amyloid angiopathy. Ann Neurol, 2005, 58(3): 459-462.
57. Charidimou A, Peeters A, *et al*. Spectrum of transient focal neurological episodes in cerebral amyloid angiopathy: multicentre magnetic resonance imaging cohort study and meta-analysis. Stroke 2012b; 43: 2324-30.
58. Calviere L, Cuvinciuc V, *et al*. Acute convexity subarachnoid hemorrhage related to cerebral amyloid angiopathy: clinicoradiological features and outcome. J Stroke Cerebrovasc Dis 2016; 25: 1009-16.

59. Charidimou A, Peeters AP, *et al*. Cortical superficial siderosis and intracerebral hemorrhage risk in cerebral amyloid angiopathy. Neurology 2013c; 81: 1666-73.
60. Linn J, Halpin A, *et al*. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. Neurology 2010; 74: 1346-50.
61. Carcel C, Sato S, *et al*. Blood pressure management in intracranial hemorrhage: current challenges and opportunities. Curr Treatment Options Cardiovasc Med 2016; 18: 22.
62. Moulin S, Labreuche J, *et al*. Dementia risk after spontaneous intracerebral haemorrhage: a prospective cohort study. Lancet Neurol 2016; 15: 820-9.
63. Kovari E, Herrmann FR, Hof PR, Bouras C. The relationship between cerebral amyloid angiopathy and cortical microinfarcts in brain ageing and Alzheimer's disease. Neuropathol Appl Neurobiol 2013; 39: 498-509.
64. Yeh SJ, Tang SC, *et al*. Pathogenetical subtypes of recurrent intracerebral hemorrhage: designations by SMASH-U classification system. Stroke, 2014, 45(9): 2636-2642.
65. Dominique Leitner, Tomas Kavanagh, *et al*. Differences in the cerebral amyloid angiopathy proteome in Alzheimer's disease and mild cognitive impairment. Acta Neuropathol. 2024 Jul 22;148(1):9.
66. Filippi M, Cecchetti G, Spinelli EG, *et al*. Amyloid-related imaging abnormalities and β-amyloid-targeting antibodies: a systematic review. JAMA Neurol, 2022,79(3):291-304.
67. Hampel H, Elhage A, Cho M, *et al*. Amyloid-related imaging abnormalities (ARIA): radiological, biological and clinical characteristics. Brain, 2023,146(11):4414-4424.
68. Chen SJ, Tsai HH, *et al*. Advances in cerebral amyloid angiopathy imaging. Ther Adv Neurol Disord, 2019, 12: 1756286419844113.
69. Farid K, Charidimou A, *et al*. Amyloid positron emission tomography in sporadic cerebral amyloid angiopathy: a systematic critical update. Neuroimage Clin, 2017, 15: 247-263.
70. KlunkWE, EnglerH, NordbergA, *et al*. Imaging brain amyloid in Alzheimer′s disease with Pittsburgh compound-B. Ann Neurol, 2004, 55(3): 306-319.
71. Rowe CC, Ackerman U, Browne W, *et al*. Imaging of amyloid beta in Alzheimer′s disease with ^{18}F-BAY94-9172, a novel PET tracer: proof of mechanism. Lancet Neurol, 2008, 7(2): 129- 135.
72. Wong DF, Rosenberg PB, Zhou Y, *et al*. In vivo imaging of amyloid deposition in Alzheimer disease using the radioligand ^{18}F-AV-45 (florbetapir [corrected] F 18). J Nucl Med, 2010, 51(6): 913- 920.
73. Serdons K, Terwinghe C, Vermaelen P, *et al*. Synthesis and evaluation of ^{18}F-labeled 2-phenylbenzothiazoles as positron emission tomography imaging agents for amyloid plaques in Alzheimer′s disease. J Med Chem, 2009, 52(5): 1428- 1437.
74. Charidimou A, Farid K, *et al*. Amyloid-PET burden and regional distribution in cerebral amyloid angiopathy: a systematic review and meta-analysis of biomarker performance. J Neurol Neurosurg Psychiatry, 2018, 89(4): 410-417.
75. Charidimou A, Farid K, *et al*. Amyloid-PET in sporadic cerebral amyloid angiopathy: a diagnostic accuracy meta-analysis. Neurology, 2017, 89(14): 1490-1498.
76. Johnson KA, Gregas M, *et al*. Imaging of amyloid burden and distribution in cerebral amyloid angiopathy. Ann Neurol, 2007, 62(3): 229-234.
77. Ly JV, Donnan GA, *et al*. 11C-PIB binding is increased in patients with cerebral amyloid angiopathy-related hemorrhage. Neurology, 2010, 74(6): 487-493.
78. Li X, Wang X, Su L, *et al*. Sino Longitudinal Study on Cognitive Decline (SILCODE): protocol for a Chinese longitudinal observational study to develop risk prediction models of conversion to mild cognitive impairment in individuals with subjective cognitive decline. BMJ Open, 2019, 9(7): e028188.
79. Cecilia Boccalini, Federica Ribaldi, *et al*. The impact of tau deposition and hypometabolism on cognitive impairment and longitudinal cognitive decline. Alzheimers Dement. 2024 Jan;20(1):221-233.
80. Emma M Coomans, Danielle van Westen, *et al*. Interactions between vascular burden and amyloid-β pathology on trajectories of tau accumulation. Brain. 2024 Mar 1;147(3):949-960.
81. van Etten ES, Verbeek MM, van der Grond J, *et al*. β-Amyloid in CSF: biomarker for preclinical cerebral amyloid angiopathy. Neurology, 2017, 88(2): 169-176.
82. Charidimou A, Friedrich JO, Greenberg SM, *et al*. Core cerebrospinal fluid biomarker profile in cerebral amyloid angiopathy: a meta-analysis. Neurology, 2018, 90(9): e754-e762.

83. Andreas Zellner, Stephan A Müller, *et al*. Proteomic profiling in cerebral amyloid angiopathy reveals an overlap with CADASIL highlighting accumulation of HTRA1 and its substrates. Acta Neuropathol Commun. 2022 Jan 24;10(1):6.
84. Theophania Ashleigh, Russell H Swerdlow, M Flint Beal. The role of mitochondrial dysfunction in Alzheimer's disease pathogenesis. Alzheimers Dement. 2023 Jan;19(1):333-342.
85. Christina Ising, Carmen Venegas 1, *et al*. NLRP3 inflammasome activation drives tau pathology. Nature. 2019 Nov;575(7784):669-673.
86. Benjamin Falcon, Jasenko Zivanov, et al. Novel tau filament fold in chronic traumatic encephalopathy encloses hydrophobic molecules. Nature. 2019 Apr;568(7752):420-423.
87. Yuting Nie, Changbiao Chu, *et al*. Lipid metabolism and oxidative stress in patients with Alzheimer's disease and amnestic mild cognitive impairment. Brain Pathol. 2024 Jan;34(1):e13202.
88. Stephen Salloway, Spyros Chalkias, *et al*. Amyloid-Related Imaging Abnormalities in 2 Phase 3 Studies Evaluating Aducanumab in Patients With Early Alzheimer Disease. JAMA Neurol. 2022 Jan 1;79(1):13-21.
89. John R Sims, Jennifer A Zimmer, *et al*. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA. 2023 Aug 8;330(6):512-527.
90. Reisa A Sperling, Michael C Donohue, *et al*. Trial of Solanezumab in Preclinical Alzheimer's Disease. N Engl J Med. 2023 Sep 21;389(12):1096-1107.
91. Greenberg SM, Rebeck GW, *et al*. Apolipoprotein E epsilon 4 and cerebral hemorrhage associated with amyloid angiopathy. Ann Neurol. 1995;38(2):254-9.
92. Racke MM, Boone LI, *et al*. Exacerbation of cerebral amyloid angiopathy-associated microhemorrhage in amyloid precursor protein transgenic mice by immunotherapy is dependent on antibody recognition of deposited forms of amyloid beta. J Neurosci. 2005;25(3):629-36.
93. Piazza F, Greenberg SM, *et al*. Anti-amyloid beta autoantibodies in cerebral amyloid angiopathy-related infammation: implications for amyloid-modifying therapies. Ann Neurol. 2013;73(4):449-58.
94. Boche D, Zotova E, *et al*. Consequence of Abeta immunization on the vasculature of human Alzheimer's disease brain. Brain. 2008;131(Pt 12):3299-310.
95. Nicholas J Reish, Pouya Jamshidi, Multiple Cerebral Hemorrhages in a Patient Receiving Lecanemab and Treated with t-PA for Stroke. N Engl J Med. 2023 Feb 2;388(5):478-479.