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Cerebral amyloid angiopathy and Alzheimer disease — one peptide, two pathways

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Abstract

The shared role of amyloid-β (Aβ) deposition in cerebral amyloid angiopathy (CAA) and Alzheimer disease (AD) is arguably the clearest instance of cross-talk between neurodegenerative and cerebrovascular processes. The pathogenic pathways of CAA and AD intersect at the levels of Aβ generation, its circulation within the interstitial fluid and perivascular drainage pathways and its brain clearance, but diverge in their mechanisms of brain injury and disease presentation. Here, we review the evidence for and pathogenic implications of interactions between CAA and AD. Both pathologies seem to be driven by impaired Aβ clearance, creating conditions for a self-reinforcing cycle of increased vascular Aβ, reduced perivascular clearance and further CAA and AD progression. Despite the close relationship between vascular and plaque Aβ deposition, several factors favour one or the other, such as the carboxy-terminal site of the peptide and specific co-deposited proteins. Amyloid-related imaging abnormalities that have been seen in trials of anti-Aβ immunotherapy are another probable intersection between CAA and AD, representing overload of perivascular clearance pathways and the effects of removing Aβ from CAA-positive vessels. The intersections between CAA and AD point to a crucial role for improving vascular function in the treatment of both diseases and indicate the next steps necessary for identifying therapies.

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Author contributions

S.M.G., M.H.-G., J.P. and S.J.v.V wrote the article. All authors made substantial contributions to discussion of the content and reviewed and edited the manuscript before submission.

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ToC summary

Amyloid-β deposition underlies the pathogenesis of cerebral amyloid angiopathy (CAA) and Alzheimer disease (AD), but the disease pathways differ. Here, Greenberg et al. consider the interactions between CAA and AD, the factors that determine which disease pathway transpires, and the implications for therapeutic development.

Introduction

The contemporary understanding of age-related cognitive impairment centres on the interplay between neurodegenerative disease and cerebrovascular disease. A substantial body of literature suggests that cognitive impairment in the ageing brain is typically driven by overlapping neurodegenerative and cerebrovascular pathologies[1]. This overlap is demonstrated by findings from the clinical–pathological Religious Orders Study and Memory and Aging Project[2], in which Alzheimer disease (AD) pathology was the most prevalent pathology (present in ~65% of brains), but four of the next five most prevalent were vascular pathologies: gross ischaemic infarcts, moderate-to-severe cerebral amyloid angiopathy (CAA), atherosclerosis and arteriolosclerosis. Each of the vascular pathologies was present in >30% of brains. When present, each accounted for a mean of 20–30% of an individual's age-related cognitive decline. Knowledge that overlap between neurodegenerative and vascular pathologies has a role in cognitive impairment affects prevention strategies. Indeed, over the past 3–4 decades, the age-specific incidence of dementia in developed countries has declined[3] in parallel with improvements in blood pressure control and vascular health, suggesting that that these improvements have at least partly reduced the vascular contribution to cognitive impairment and dementia (VCID).

Interactive effects of neurodegenerative and cerebrovascular disease on cognition certainly result from the cumulative brain injuries caused by each process. However, at a more mechanistic level, the two processes might also interact through cross-talk between neurodegenerative pathways and the blood vessels[4]. The most clear-cut examples of mechanistic interactions are seen in CAA and AD. CAA involves cerebrovascular deposition of amyloid-β (Aβ), which is also the primary constituent of neuritic plaques in AD (Fig. 1). The two conditions often overlap, presumably because of the shared role of Aβ. CAA might also contribute to the pathogenesis of AD by affecting perivascular drainage, a major route of Aβ clearance from the brain[5]. Given that overlap between sporadic CAA and AD is high[6,7], virtually every clinical trial of treatment for sporadic AD or CAA can be considered as a trial for treatment of both, underlining the importance of identifying the interactions between these two processes in disease pathogenesis.

In this Review, we summarize the current understanding of the relationship between CAA and AD, how the common factor of Aβ deposition can generate two different disease pathways, how each pathology affects the other, and how the two pathologies together promote cognitive impairment and neurological dysfunction. We focus on the pathological and pathogenic similarities and differences between CAA-related and AD-related brain injury, the central role of perivascular clearance in accumulation of Aβ in the brain, the biochemical and genetic features that favour deposition of Aβ in the vessels or in plaques,

and the potential role of CAA in the development of amyloid-related imaging abnormalities (ARIA) that have been identified as major adverse effects of anti-Aβ immunotherapy.

Brain injury in CAA and AD

CAA and AD pathology frequently co-occur in the same brain, presumably because Aβ is pathogenic in both. For example, in an autopsy analysis of 404 brains from individuals in the Religious Orders Study (mean age at death 86.5 ± 7.0 years), the correlation coefficient between CAA severity and AD severity was 0.68 (ref.[6]). Another autopsy study of 3,976 brains in the US National Alzheimer's Coordinating Center database (mean age at death 83.2 ± 8.4 years) revealed that the pathological grade of CAA was moderate to severe in 5.3% of brains with no neuritic plaques, 16.1% of brains with mild neuritic plaques, 31.7% of brains with moderate neuritic plaques, and 45.3% of brains with severe neuritic plaques[7]. Similarly, use of lobar cerebral microbleeds as a neuroimaging marker of CAA[8] has shown that the prevalence and incidence of these lesions is increased in symptomatic patients with AD and cognitively normal individuals who are positive for Aβ on PET imaging, suggesting that CAA-related vessel rupture occurs in the presence as well as the absence of AD[9]. These examples show that, though CAA and AD do not occur in perfect lockstep[7], their co-occurrence far exceeds that of other vascular and neurodegenerative pathologies.

The mechanisms by which AD and CAA lead to brain injury largely do not seem to overlap, however. The precise mechanisms of AD-related brain injury remain unclear[10], but seem to centre on Aβ-triggered loss of synapses and neurons, normally measured as a loss of cortical tissue, and the development of hyperphosphorylated tau-containing neurofibrillary lesions, which can now be detected with PET[11,12,13]. Each measure correlates with cognitive performance in Aβ-positive individuals[14,15].

By contrast, CAA-related brain injuries seem to arise from blood vessel dysfunction[16], either via loss of vessel integrity and haemorrhage or via loss of normal blood supply and ischaemia. CAA-related haemorrhagic lesions include large symptomatic intracerebral haemorrhages, small (mostly asymptomatic) cerebral microbleeds, and bleeding into the cortical sulci (convexity subarachnoid haemorrhage or cortical superficial siderosis). T2*-weighted MRI detects these haemorrhagic markers with high sensitivity, enabling them to form the basis of the Boston Criteria for CAA[8]. The primary non-haemorrhagic (presumed ischaemic) forms of brain injury in CAA show up as white matter hyperintensities on T2-weighted MRI, structural disconnection measured with diffusion-tensor MRI, and cerebral microinfarcts. These non-haemorrhagic brain injuries, particularly loss of structural connectivity[17], seem to correlate most directly with cognitive impairment and slower gait speed in CAA, suggesting that disconnection has a primary role in vascular cognitive impairment and dementia[18]. A recent investigation of the underlying anatomical basis of reduced structural connectivity in CAA revealed potential contributions from axonal loss, myelin loss and cerebral microinfarcts[19]; the latter is the most difficult to detect in vivo but is likely to be the most abundant focal CAA-related brain lesion[20]. Besides overt vascular or perivascular inflammation associated with an autoimmune subtype of CAA[21], inflammation does not seem to be a major component in CAA-related microhaemorrhage or microinfarction[22].

Despite the broad distinctions between neurodegenerative brain injury in AD and vascular brain injury in CAA, evidence suggests some overlap in pathogenic mechanisms. For example, cerebrovascular dysfunction, which is one of the earliest detectable abnormalities in sporadic and hereditary CAA[23–25], has also been identified as an early step in AD pathogenesis[26]. Conversely, tau deposition is generally not a prominent feature of CAA pathology but has been observed around Aβ-laden vessels in sporadic and hereditary CAA[27]. In addition, brain atrophy and cortical thinning seem not to be AD-specific neuroimaging markers but also features of cerebrovascular disease, including CAA[28]. From a clinical standpoint, the presence of advanced CAA in AD is associated with greater cognitive impairment[29] and/or faster cognitive decline[30], indicating shared contributions to clinical dysfunction.

Pathogenic mechanisms

Aβ clearance pathways

Pathways that are known to be involved in clearing soluble Aβ from the brain include transport across the blood–brain barrier (BBB), phagocytosis, enzymatic degradation and perivascular drainage[5]. The extent to which each of these pathways contributes to elimination of Aβ from the brain is unclear, but abnormal perivascular drainage of Aβ from interstitial fluid is believed to have a major role in the pathogenesis of CAA and AD.

In studies published in the 1980s and 1990s, injection of tracers into the brains of rats revealed that interstitial fluid drains alongside intracortical arterioles and leptomeningeal arteries and ends up in extracranial lymph nodes[31–33]. Neuropathological studies of brains from patients with AD have shown that accumulation of Aβ around arteries is fivefold more common than around veins and that Aβ is first deposited at the periphery of arterioles, at the site of putative interstitial fluid drainage pathways[34]. These observations support the hypothesis that Aβ exits the brain via perivascular pathways and that reduced perivascular clearance (rather than overproduction of Aβ) is a shared pathogenic mechanism in CAA and AD[34–36]. Further tracer studies of this putative exit route have suggested that fluid gathers around capillaries and leaves the brain along intramural peri-arterial drainage (IPAD) pathways between the smooth muscle cell basement membranes in the tunica media of arterioles and arteries[37,38]; these pathways match the predominant distribution of Aβ deposition in CAA[39].

An alternative proposed route of perivascular drainage of the interstitial fluid is via the glymphatic system[40–42]. This pathway, which has mainly been described in the context of cerebrospinal fluid (CSF)–interstitial fluid exchange, involves CSF entering the brain alongside arteries, mixing with interstitial fluid and exiting the brain alongside veins. The movement of fluid might depend on the astrocytic water channel aquaporin-4, which serves as the primary channel for convective flow of fluid from the peri-arterial space into the interstitial space and ultimately the peri-venous compartment[43–45]. Experiments in aquaporin-4 knockout mice and postmortem human brain tissue showed that tracer clearance was reduced in the absence of aquaporin-4 and aquaporin-4 levels were reduced in astrocytic endfeet in the presence of CAA, suggesting that glymphatic clearance can fail in AD and

CAA as a result of aquaporin-4 mislocalization and a consequent decrease in Aβ clearance[45,46].

Differing findings about the specific patterns of drainage (peri-arterial or peri-venous) in IPAD and the glymphatic system could be attributed to different experimental procedures (reviewed elsewhere[47,48], and this remains a topic for ongoing studies[38,45,47,49]. The two mechanisms could coexist for different types of convective fluid movements. Both models indicate the importance of perivascular drainage pathways in the pathophysiology of CAA and AD, although IPAD better fits the pattern of Aβ deposition observed in vessels in post-mortem human brains.

Despite consensus that fluid drainage from the brain relies on cardiac output[37,49], the exact mechanism responsible for perivascular clearance is incompletely understood. Arterial pulsations generated by the heart have been suggested as a potential motive force[49–52], but other models have suggested that these small pulsations cannot create the necessary gradient to push fluid towards the pial surface along arteries (or veins)[53,54]. An alternative is vasomotion generated by larger, spontaneous, low-frequency contractions and dilations of smooth muscle cells[55,56], and a role for this motive force is supported by accumulating evidence[54,57]. Additional studies are needed to unravel the contributions of arterial pulsations and vasomotion[58], and advances in contrast-enhanced MRI could improve visualization of clearance pathways in humans in vivo[59,60], an important development towards translating experimental observations to the clinical setting.

Interference with perivascular clearance as a result of vascular Aβ deposition in CAA could establish a self-reinforcing cycle of reduced clearance, increased Aβ deposition, and consequent loss of vascular smooth muscle cells (Fig. 2). This self-reinforcing mechanism would exacerbate AD pathology, owing to reduced Aβ clearance, and CAA-related vessel wall breakdown, vascular lesions and tissue injury. In vivo studies have shown that perivascular clearance and evoked vascular reactivity (functional hyperaemia) is reduced in mice with CAA[57,61,62]. In patients with CAA, reduced evoked vascular reactivity in response to visual stimulation has also been observed, assessed by measurement of the blood-oxygen-level dependent signal in the visual cortex[23–25]. Further evidence for reduced perivascular clearance in patients with CAA comes from observation of abnormally enlarged perivascular spaces in the subcortical white matter on in vivo MRI[63,64], correlating with a high Aβ burden in the overlying cortex[65]. Furthermore, topographical colocalization of enlarged perivascular spaces and cortical microbleeds has been observed in patients with CAA[66].

Several vascular pathologies other than CAA also seem to impair perivascular clearance and could be important in the pathophysiology of AD and CAA. For example, impaired clearance was observed in mice after induced transient hypertension[49], vessel occlusions or microinfarcts[61,67,68], in line with observations that capillary CAA downstream of occluded arterioles was increased in human post-mortem tissue[69]. Furthermore, the detrimental effects of vascular pathologies on Aβ clearance from the brain are probably exacerbated by ageing, which involves thickening of vessel walls and reductions in vasoactivity[68,70,71]. Evidence from mouse and human studies suggests that clearance is also affected by disrupted sleep

cycles[72,73], with sleep deprivation causing increased brain concentrations of Aβ[74,75]. A proposed explanation for these intriguing findings is that sleep induces increases in interstitial space volume, leading to increased efflux of solutes, including Aβ[72]. Therefore, prevention of age-related vascular dysfunction and cerebrovascular pathologies at an early age and promotion of healthy sleep habits are plausible approaches to maximizing perivascular clearance and delaying onset of Aβ accumulation in the brain. Similarly, therapeutic targeting of vascular smooth muscle cells is an interesting possibility for promoting healthy perivascular clearance, thereby reducing the risk of AD and cognitive decline with increasing age.

Aβ deposition

Neuropathological evidence shows that Aβ is initially deposited in the neocortex of the brain as CAA and as parenchymal plaques[76,77]. Parenchymal pathology subsequently expands into the allocortex, thalamus and basal ganglia, whereas vascular Aβ spreads to allocortical areas and the cerebellum[76,77]. Leptomeningeal and parenchymal blood vessel Aβ deposition usually affects the posterior lobar brain regions (particularly occipital) and rarely affects the deep grey nuclei, white matter and brainstem[77]. When Aβ deposition occurs in brain capillaries, the condition is classified as CAA type I; CAA without capillary involvement is classified as CAA type II[78]. CAA type I tends to be widespread, especially in the neocortex and hippocampus[77,79]. CAA type I has been specifically associated with neuritic plaques and severe AD pathology[79,80].

The characteristically patchy and segmental distribution of CAA pathology[81] suggests that vascular Aβ preferentially accumulates at sites of initial Aβ deposition, or ‘seeding’. This preferential accumulation has been observed directly in transgenic mice by use of serial in vivo imaging of CAA progression[82]. More explicit evidence for a prion-like role of Aβ seeds in triggering CAA comes from animal[83] and human[84,85] studies in which exogenous exposure to Aβ from sources such as pituitary gland extract or a cadaveric graft can trigger early onset CAA. These findings suggest that amyloid seeding and subsequent expansion is a mechanism of initiation and progression of sporadic CAA, though on the basis of anecdotal evidence, exposure to contaminated tissue as a cause of CAA seems to be extremely rare.

Aβ peptide length—Although Aβ is the main component of neuritic plaques and of CAA pathology, the length of Aβ peptides that form the deposits seems to differ between the lesions (Table 1). Peptides that extend to carboxy position 42 ($A\beta_{42}$) are mainly deposited in neuritic plaques, whereas shorter $A\beta_{40}$ peptides are the predominant forms deposited in the walls of leptomeningeal and cortical arteries and, occasionally, veins[86–88]. Vascular deposits also contain $A\beta_{42}$, but the $A\beta_{40}$:$A\beta_{42}$ ratio is higher than that in plaques[89]. However, the $A\beta_{40}$:$A\beta_{42}$ ratio in capillary deposits is lower than in arteries and veins, and is equivalent to that in neuritic plaques[89,90].

The mechanisms that underlie preferential deposition of $A\beta_{40}$ in vessel walls and $A\beta_{42}$ in plaques and capillaries have not yet been elucidated. One hypothesis is that vascular Aβ originates from a different source to Aβ in plaques and is generated locally, principally in

smooth muscle cells[91,92]. However, evidence from transgenic mouse models demonstrates that Aβ with a common neuronal origin can cause CAA and parenchymal Aβ plaques[93,94], indicating that neuron-derived Aβ can migrate to and accumulate in the vasculature far from its production site. Given that $A\beta_{42}$ is less soluble and forms fibrils faster than shorter Aβ peptides[95], it is more likely to be retained in the parenchyma and initiate insoluble plaque nucleation. By contrast, the more soluble $A\beta_{40}$ can diffuse along perivascular drainage pathways to accumulate in the walls of vessels. Nevertheless, evidence suggests that $A\beta_{42}$ is still the first species to be deposited in the vessel wall[96]. Other Aβ variants, including N-terminal and C-terminal truncated Aβ peptides and species that contain post-translational modifications (Table 1), have also been identified in human brain tissue, though no specific pathogenic role in CAA has yet been identified for any of these variants. Various analytical methods suggest that truncated Aβ species and Aβ that is pyroglutamate-modified at Glu-3 segregate similarly to full-length, unmodified peptides, whereas species that end at position 41 or before are preferentially deposited in vessels[88,97].

Genetic influences—Mutations in the *APP* gene that encodes amyloid precursor protein can also determine the conformation and deposition sites of Aβ (Table 1). Mutations in *APP* that flank the Aβ coding region generally increase relative or total levels of $A\beta_{42}$ and therefore predispose to formation of neuritic plaques and phenotypes associated with early onset AD[98]. By contrast, *APP* mutations located within or just outside the Aβ coding region induce a clinicopathological phenotype of prominent CAA. Such a mutation causes the autosomal dominant disorder of Dutch-type hereditary CAA (D-CAA, also known as hereditary cerebral haemorrhage with amyloidosis — Dutch type), which is clinically characterized by early-onset recurrent haemorrhagic strokes and dementia[99]. The cause is a nucleotide change at *APP* codon 693 that results in a single amino acid substitution (Glu693Gln) at Aβ position 22 (ref.[100]). In patients with D-CAA, leptomeningeal and cortical blood vessels are affected by severe CAA with diffuse parenchymal Aβ deposits but few or no dense-core plaques[101].

Other mutations have also been identified at Aβ position 22, including the Artic mutation (Glu693Gly)[102], the Italian (Glu693Lys)[103] mutation, and mutations have also been identified at Aβ positions 21, 23 and 34 within the Aβ sequence, — the Flemish (Ala692Gly)[104], Iowa (Asp693Asn)[27] and Piedmont (Leu705Val)[105] mutations, respectively. Each of these variants causes a common neuropathological phenotype characterized by severe CAA, and the Arctic and Flemish mutations also result in parenchymal fibrillar Aβ deposits[106,107]. Notably, in patients who carry these familial variants, predominant deposition of $A\beta_{40}$ species is usually seen in cortical and leptomeningeal arteries without an overall increase in Aβ production[103,107–109], also the case in sporadic CAA. The clinical spectrum of these familial CAA forms varies, and includes cerebral haemorrhages, ischaemic brain injury and dementia[103,105,110,111].

Extensive investigations have been conducted to determine the pathogenic mechanisms that explain the differences in phenotypes induced by the vasculotropic Aβ peptides[112–116]. This work has shown that the Aβ peptide that contains the Dutch substitution (AβDutch) forms more fibrils in vitro than the wild-type peptide[112,117] and assembles on the surface of cerebrovascular smooth muscle cells, where it induces a pathological response, owing the

abnormal charge of the peptide[113]. Results of other studies have shown that AβDutch is more resistant to proteolytic degradation[118,119] and less efficiently cleared across the BBB than wild-type Aβ[120]. Observations from a transgenic mouse model of D-CAA further suggest that the Dutch mutation promotes Aβ deposition in the cerebral vasculature, possibly by increasing the Aβ :$Aβ_{42}$ ratio[94,115] through a currently undefined mechanism.

Increased *APP* gene dosage also seems to be sufficient to induce CAA; the condition develops with high penetrance and relatively early onset among individuals with *APP* duplication[121,122] or Down syndrome (in which the chromosome that carries *AAP* is present in three copies)[123]. In addition, prominent vascular Aβ deposition has been observed in some patients with familial AD who have mutations in the *PSEN1* or *PSEN2* genes, which encode presenelin-1 and presenelin-2, respectively[124–126]. Evidence suggests that mutations in *PSEN1* at positions beyond codon 200 cause more severe CAA pathology[127] and more parieto-occipital white matter hyperintensities on MRI[128] than do mutations at positions before codon 200, raising the possibility that particular alterations in presenilin activity favour vascular Aβ pathology.

APOE is the only susceptibility locus for sporadic CAA that has been identified consistently in genetic analyses[129,130]. In these analyses, CAA has generally been identified according to lobar location of intracerebral haemorrhage rather than by MRI detection of strictly lobar microbleeds, as the requirement for MRI would limit sample size. As a consequence, the results might be affected by diagnostic misclassification. Another approach has been to analyse correlates of CAA pathology in postmortem brains, but two such studies have produced discordant results.

Analysis of 2,807 brains with pathologically graded CAA found an association with APOE but no other loci identified in genome-wide association studies (GWAS) and none of 21 AD-linked loci identified in previous GWAS[131]. Another candidate-gene analysis of 29 AD risk loci in 256 brains from individuals aged ≥85 years found at least nominal (P <0.05) associations (including results from imputed genotypes) of 20 loci with noncapillary CAA and 15 with capillary CAA; both pathological measures were strongly associated with *APOE*[132]. Determining the basis for the differences in these results represents an important question for future large-scale studies.

Co-deposited proteins and apolipoproteins—Aβ that is deposited in neuritic plaques and vessels is accompanied by Aβ-associated proteins, including complement proteins, serum amyloid P component, α1-antichymotrypsin, glycosaminoglycans, matrix metalloproteinase 9 (MMP9) and various apolipoproteins, such as apolipoprotein E, apolipoprotein J (also known as clusterin) and apolipoprotein A-I[133–145] (Table 1). When, how and at what concentrations these associated proteins are co-deposited with Aβ remain to be determined, but some of these components can accelerate or inhibit the formation of Aβ fibrils[146–150].

Apolipoprotein E is a principal component of both neuritic plaques and CAA[151,152] and has been implicated in the pathogenesis of these disorders by evidence that the *APOE**ε4 allele is a major risk factor for both AD[153,154] and CAA[155,156], that *APOE**ε4 is associated with

total and vascular Aβ levels[157] and that *APOE** ε2 is a risk factor for haemorrhagic CAA[153–155]. The *APOE**ε2 allele is protective in AD[158]. The mechanistic basis of these associations might relate to the fact that binding of Aβ to apolipoprotein E modulates clearance of the peptide across the BBB[159]. Evidence suggests that this process is apolipoprotein E isoform-specific — apolipoprotein E ε4 tends to change the pathway of Aβ clearance from the low-density lipoprotein receptor-related protein 1 (LRP1) pathway to the less efficient very-low-density lipoprotein (VLDL) receptor, whereas apolipoprotein E ε2 and ε3 mediate faster clearance via both LRP1 and VLDL receptor[159]. Other proposed mechanisms for apolipoprotein E isoform-specific effects on Aβ deposition include direct competition for clearance pathways[160], effects on peptide aggregation and fibrillogenesis[161], and inhibition of Aβ-induced MMP9 activity[162].

The absence of murine apolipoprotein E in a mouse model of cerebral β-amyloidosis delayed parenchymal deposition of fibrillar Aβ and development of CAA[163,164], but the expression of human apolipoprotein E in other transgenic mouse lines prevented Aβ accumulation through a mechanism that depended on the apolipoprotein E isoform[165,166]. Further studies found that expression of mutant amyloid precursor protein and human apolipoprotein E ε4 in mice led to redistribution of Aβ deposition to the cerebral vessels[167], and analysis of mouse apolipoprotein E and human apolipoprotein E ε4 in the same transgenic mouse brain showed that mouse apolipoprotein E co-localized with plaques whereas human apolipoprotein E ε4 co-localized with and promoted cortical (though not leptomeningeal) CAA[168]. In addition to confirming that mouse and human apolipoprotein E differ, the latter study suggests that apolipoprotein E is differentially involved in the formation of plaques or CAA in blood vessels at different locations. Interestingly, *APOE* genotype seems to influence Aβ deposition in different blood vessel types in the human brain—*APOE**ε4 expression is associated with capillary CAA type I, whereas *APOE**ε2 expression is associated with CAA type II[78,169].

As is the case for apolipoprotien E, apolipoprotein J is co-deposited with fibrillar Aβ in cerebrovascular and parenchymal lesions[141,170,171]. Apolipoprotein J interacts with Aβ to prevent Aβ aggregation[146,172,173], an effect that reportedly depends on the Aβ:apolipoprotein J ratio[174]. In a study of the APP–presenilin 1 transgenic mouse model, apolipoprotein J deficiency reduced the number of parenchymal Aβ plaques and increased vascular Aβ deposition[175]. Apolipoprotein J also regulated Aβ clearance from the brain, as previously proposed[176], and its absence could impair Aβ clearance across the BBB, leading to its accumulation in perivascular drainage spaces and more CAA pathology[175]. In other transgenic AD mouse models, apolipoprotein J deficiency decreased parenchymal fibrillary Aβ, but the shift to cerebrovascular Aβ deposition in the absence of apolipoprotein J was not seen[177,178].

Quantitative proteomic analysis of isolated neuritic plaques from patients with AD have verified the involvement of proteins previously associated with Aβ and also identified novel components[179,180], most of which have not yet been investigated in CAA. Proteomic analysis of vascular amyloid has confirmed the presence and abundance of apolipoprotein E or apolipoprotein J in leptomeningeal and cortical vessels from the brains of patients with CAA[150,181,182]. Other potentially important proteins that were identified in these studies as

being associated with vascular amyloid but not with neuritic plaques include metalloproteinase inhibitor 3[181], norrin, collagen α-2 (VI) chain[182] and sushi repeat-containing protein 1 (SRPX1)[183]. Some of these co-localized proteins suggest mechanisms that contribute to vessel injury, such as the ability of SRPX1 to increase $A\beta_{40}$-induced caspase activity[183], but the pathogenic roles of these proteins, if they have any, are unknown. Deposition of fibrinogen — a precursor of fibrin and a principal contributor to haemostasis — has also been detected in CAA-positive vessels in AD[184], and the extent of deposition was greatest in people who were homozygotic for *APOE**ε4 (ref.[185]). In transgenic mouse models, depletion of fibrinogen decreased CAA pathology and cognitive decline[184], further suggesting a contribution to vascular amyloid deposition.

CAA and ARIA

ARIA, which can be detected with MRI, are vascular abnormalities that have been seen as a consequence of Aβ-targeted immunotherapy in trials in AD[186–187]. ARIA are classified into two subtypes[186]: ARIA-E is characterized by fluid attenuation inversion recovery (FLAIR) MRI hyperintensities that are consistent with vasogenic oedema and sulcal effusions with occasional gyral swelling, whereas ARIA-H is characterized by parenchymal microbleeds and superficial haemosiderin deposition in the leptomeninges, seen on T2*-weighted MRI. ARIA-E typically resolves on imaging over the course of weeks, whereas ARIA-H typically remains on subsequent MRIs. The mechanisms that underlies ARIA are not fully understood, but the available evidence suggests that antibody-mediated breakdown of neuritic plaques releases Aβ that is then deposited in vessels, leading to increased CAA, perivascular inflammation, and/or impaired perivascular clearance.

ARIA and amyloid-β clearance

ARIA have now been observed in multiple passive immunotherapy trials, most prominently in trials of antibodies that target N-terminal or conformational forms of Aβ and that have cleared neuritic plaques. In trials of bapineuzumab, gantenerumab and aducanumab, the incidence of ARIA-E was dose-dependent and *APOE**ε4-dependent[187–188]. In the trial of bapineuzumab, the incidence among people without the *APOE**ε4 allele reached 14.2% with the highest dose, whereas the incidence among *APOE**ε4 carriers was 15.3%, even though these patients received only the lowest dose[187]. A higher incidence (~40%) of ARIA-E was reported with use of aducanumab and was most common among *APOE**ε4 carriers[189]. Lower rates of ARIA-E have been reported with use of antibodies that target mid-peptide and C-terminal regions of Aβ[190–192], possibly because these antibodies tend to bind to monomeric or specific oligomeric Aβ[193], thereby mobilizing less Aβ from neuritic plaques than do antibodies against the N-terminus. A low incidence (< 1%) of ARIA-E has been seen in placebo-treated trial participants and in screening populations and observational studies of autosomal dominant and sporadic AD patients; in these contexts, the condition has primarily been observed in *APOE**ε4 carriers[190,194,195].

Treatment with anti-amyloid immunotherapy is also associated with ARIA-H, though the increased incidence compared with the incidence among people who receive placebo is less pronounced than that for ARIA-E[196,188,189]. ARIA-H can also occur in the aftermath of

ARIA-E[196]. In the trial of aducanumab, the *APOE**ε4 allele was associated with higher rates of co-occurring ARIA-H and ARIA-E (35% at the highest dose)[189]. A meta-analysis of immunotherapy trials found that treatment was associated with an increased risk of any ARIA and of ARIA-E but not of ARIA-H[197]. The lack of an association with ARIA-H might reflect the fact that participants with more than four microbleeds are typically excluded from immunotherapy trials and that the rate of spontaneous incident microbleeds in observational studies is substantial[198].

Risk factors for ARIA

The risk factor profile for ARIA could provide insight into the underlying pathophysiology. The risk of ARIA-E is dependent on the antibody dose, but whether the risk is driven primarily by the highest antibody concentration reached or the rate of increasing dose is unclear; limited data suggest that dose titration reduces the risk[199,200]. Multiple studies have demonstrated an association between a higher *APOE**ε4 allele dose and a greater risk of ARIA-E and ARIA-H[196,201,202]. Furthermore, *APOE**ε4 carriers are at substantially increased risk of symptomatic ARIA, which can manifest as headache, lethargy, confusion, neuropsychiatric symptoms and, in rare cases, seizures. Symptomatic ARIA occurs in 1–20% of patients with ARIA-E, and this variability depends on the antibody used, the dose and the prevalence of *APOE**ε4[188,189,201].

Hypertension, hyperlipidaemia and diabetes seem not to be risk factors for ARIA-E[203], and no associations have been found between ARIA and baseline biomarkers of brain amyloid on PET, volumetric MRI measures or most CSF biomarkers, although lower baseline CSF levels of $A\beta_{42}$ in people without *APOE**ε4 was associated with a higher risk of ARIA[204].

ARIA and CAA

A plausible explanation for ARIA, first proposed on the basis of postmortem studies of people who received the original active immunotherapy AN1792 (refs[205]), is that solubilization of Aβ overwhelms the capacity for Aβ clearance via the perivascular CSF bulk flow pathways, leading to amyloid deposition in the arterial wall and accelerated development of CAA (Fig. 3). The fact that the number of microbleeds at baseline and the *APOE**ε4 allele are risk factors for both ARIA and CAA support this interpretation, as microbleeds suggest the presence of Aβ in vessel walls and the *APOE** ε4 allele suggests a high Aβ burden. Autopsy studies of individuals who received immunotherapy have demonstrated that CAA develops to a greater extent in cortical and leptomeningeal vessels (the locations where ARIA occurs) than untreated individuals and revealed treatment-associated concentric vessel wall splitting[206], a key element of CAA-associated vasculopathy[207]. Therapeutic antibodies against Aβ might not only accelerate vascular deposition but also bind to accessible vascular Aβ and consequently further disrupt vessel integrity, contributing to leakage of proteinaceous fluid (ARIA-E) and red blood cells (ARIA-H).

Another line of evidence that links ARIA to CAA is the resemblance of ARIA to the syndrome of CAA-related inflammation (CAA-ri). CAA-ri occurs in a subset of patients with CAA, and its clinical presentations, neuroimaging features and association with

*APOE**ε4 (refs[208,209]) are similar to those of ARIA-E. CAA-ri involves infiltration of microglia, T cells and Aβ-containing multinucleated giant cells around CAA-positive vessel segments[21], suggesting that spontaneous anti-Aβ autoimmune response occurs. In addition, CSF concentrations of autoantibodies against Aβ are increased during the active phase of CAA-ri[210], supporting the hypothesis that the process involves an anti-Aβ autoimmune response and that immunotherapy-related ARIA-E is an iatrogenic version of CAA-ri. CAA-ri is typically treated with immunosuppression, which generally improves clinical symptoms and vasogenic oedema[208] and leads to normalization of CSF anti-Aβ antibody concentrations[210].

The analogy between ARIA and with CAA-ri suggests that repeated or prolonged immunotherapy would increase the inflammatory response, but ARIA seems to decrease with longer treatment, indicating a more complex relationship. Prolonged immunotherapy treatment might lead to a progressively lower plaque burden, which would reduce amyloid mobilization and subsequent deposition in vessel walls, potentially reducing vascular inflammation and risk of ARIA.

Capillary amyloid deposition and BBB alterations are also likely to be involved in ARIA. Ultrastructural analysis of mice treated with anti-Aβ immunotherapy has revealed disruption of the vascular units that comprise the BBB; for example, the normally tight configuration of astrocyte endfeet that envelop endothelial cells is altered as a result of capillary Aβ[211]. The same study showed that capillary Aβ was associated with local loss of aquaporin 4 channels that affect extracellular–intracellular fluid flux, which could also contribute to ARIA-E. Loss of apolipoprotein J might also disrupt perivascular drainage pathways, which could, as noted above, shift amyloid deposition to the cerebrovasculature[175]. In an MRI study of *APP*-overexpressing mice that had been treated with a mouse analogue of bapineuzumab, transient BBB leakage was associated with microbleeds during early treatment, recapitulating some features of ARIA such as the frequent co-occurrence of ARIA-E and ARIA-H; this effect was not seen in saline-treated transgenic mice or immunotherapy-treated wild-type mice[212]. These results are consistent with a complex model in which ARIA results from mobilization of aggregated Aβ from the neuritic plaques of AD, which leads to vascular and perivascular Aβ deposition (that is, increased CAA), but also concurrent Aβ mobilization from vessels, which leads to disruption of smooth muscle integrity and the BBB.

Vessel recovery after ARIA

Limited evidence suggests that vessels affected by ARIA are capable of some degree of recovery. Postmortem examination of brains from people who received long-term treatment with AN1792 did not reveal vascular smooth muscle cell loss or vessel wall thinning[206]. Similarly, in transgenic mice that were exposed to an analogue of bapineuzumab for a prolonged period, variance in vascular smooth muscle cell and collagen IV extracellular matrix thickness returned to wild-type levels when treatment was stopped[211]. These results raise the (still unproven) possibility that morphology and, consequently, perivascular clearance can recover (Fig. 3). In most individuals who are diagnosed with CAA-ri and are treated with immunosuppressive drugs, clinical symptoms improve and MRI signs of

vasogenic oedema resolve,[208], which further supports the possibility of vessel recovery following anti-Aβ immune response.

Conclusions and future directions

The evidence reviewed above demonstrates that complex interactions at multiple levels exist between CAA and AD pathophysiology. Major commonalities between the conditions are the shared roles of Aβ production, metabolism and convective clearance from the interstitial fluid via the perivascular and intramural pathways. Within these intersecting pathways, multiple factors favour vascular or parenchymal Aβ deposition; these factors include $Aβ_{40}$:$Aβ_{42}$ ratio, Aβ mutations, and the presence and composition of apolipoprotein E and apolipoprotein J. The AD and CAA pathways seem to diverge with respect to how they cause tissue injury: AD pathology promotes neuronal and synaptic loss via undefined mechanisms, whereas CAA generates focal tissue lesions via haemorrhagic and ischaemic vascular brain injury.

The interactions between CAA and AD pathophysiology have several implications for treatment. The apparently central role of perivascular drainage suggests that preserving vascular structure and function would improve amyloid clearance and reduce deposition. Candidate approaches to maintaining vascular health and perivascular clearance pathways include reducing mid-life vascular risk factors[213] and improving sleep structure[73]. Effective treatment of CAA might also have the dual benefit of preventing direct CAA-related brain injury and the self-reinforcing cycle of vascular Aβ deposition that worsens Aβ clearance (Fig. 2). Interventions that worsen CAA, however, such as anti-Aβ immunotherapies that mobilize Aβ from neuritic plaques[214], might worsen vascular physiology and perivascular clearance, feeding into this self-reinforcing cycle. Clearance of Aβ from plaques into vessels is a possible mechanism for ARIA and for the observation that cerebrovascular reactivity to visual stimulation (without extensive ARIA) worsened in patients with probable CAA who were treated with the anti-Aβ antibody ponezumab[192].

These considerations indicate key steps that would substantially accelerate our understanding of the inter-relationship between CAA and AD and the role of CAA–AD crosstalk in human disease. Development of imaging methods that distinguish between plaque and vascular Aβ in living patients would enable identification of the genetic, environmental and treatment factors that favour Aβ deposition in one compartment versus the other. This goal is clearly challenging, given the close structural relationship between the two types of Aβ deposits. In experiments in an *APP* transgenic mouse model, the phenoxazine derivative resorufin preferentially bound to vascular Aβ[215], but this finding has been taken no further in mouse or human studies.

A second key goal for translational research is development of a non-invasive method for reliably measuring clearance of brain interstitial fluid. Indirect approaches, such as the somewhat invasive method of isotope labelling of Aβ[216] and PET imaging of ventricular tau[217] have suggested that clearance of interstitial fluid is reduced in patients with AD. However, these approaches are limited by the binding of isotope labeled-Aβ and the tau tracer THK5117 within the brain — an ideal ligand would exit the interstitial fluid via

perivascular drainage pathways without binding or uptake of any sort. If these challenges can be overcome, measurement of interstitial fluid clearance would enable testing of candidate treatments for slowing CAA and AD progression and possibly that of other brain diseases associated with impaired solute clearance.

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Key Points

- Amyloid-β (Aβ) in the brain interstitial fluid can be cleared via perivascular drainage pathways or deposited as neuritic plaques in the brain parenchyma or as cerebral amyloid angiopathy (CAA) along vessel walls.
- Vascular dysfunction caused by CAA reduces perivascular Aβ clearance in animal models, creating a vicious cycle of vascular and parenchymal Aβ accumulation.
- Factors that favour vascular Aβ deposition over parenchymal deposition include termination of Aβ at or before position 41, missense mutations within the Aβ coding region, and some co-deposited proteins, such as fibrinogen.
- Amyloid-related imaging abnormalities observed in trials of anti-Aβ immunotherapy, might result from mobilization of plaque Aβ into the perivascular drainage system or from antibody targeting of vascular Aβ deposits.
- Development of methods for imaging perivascular drainage in humans would be a key step towards identifying treatments for enhancing Aβ clearance and reducing vascular and parenchymal deposition.

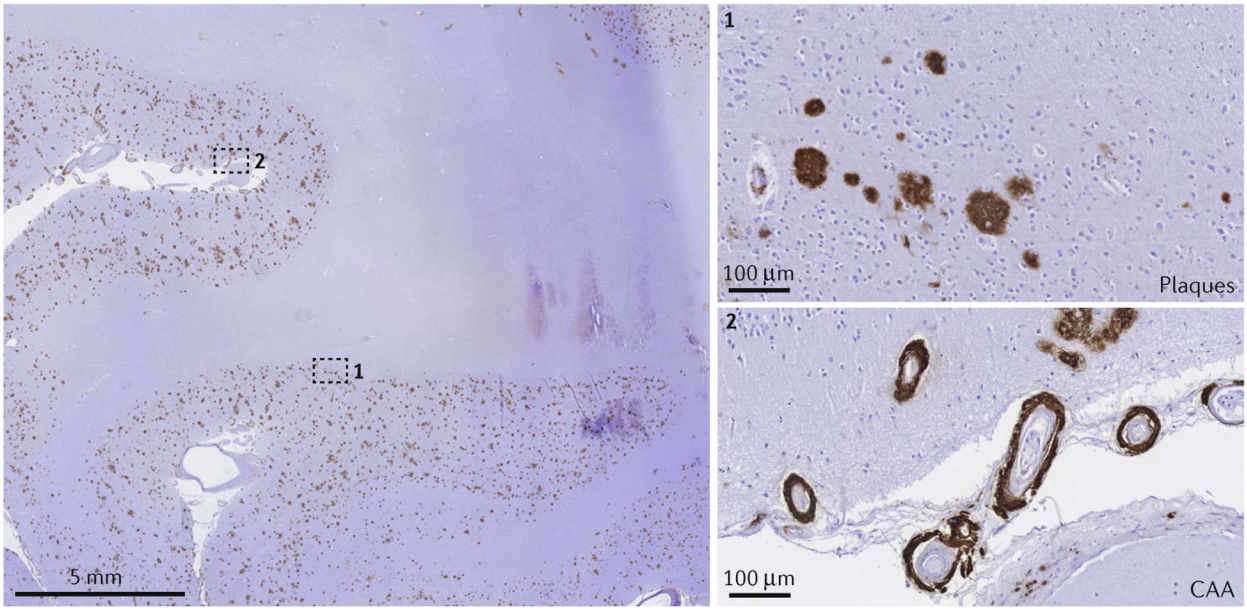

Figure 1 |.

Co-existing amyloid-β in neuritic plaques and vessel walls. Anti-amyloid-β immunostaining (clone 6F/3D, Agilent, 1:200) of a postmortem section of the occipital lobe from a 67-year-old man (left) reveals co-existing neuritic plaques (right, top) and cerebral amyloid angiopathy (CAA; right, bottom) in leptomeningeal and cortical vessels.

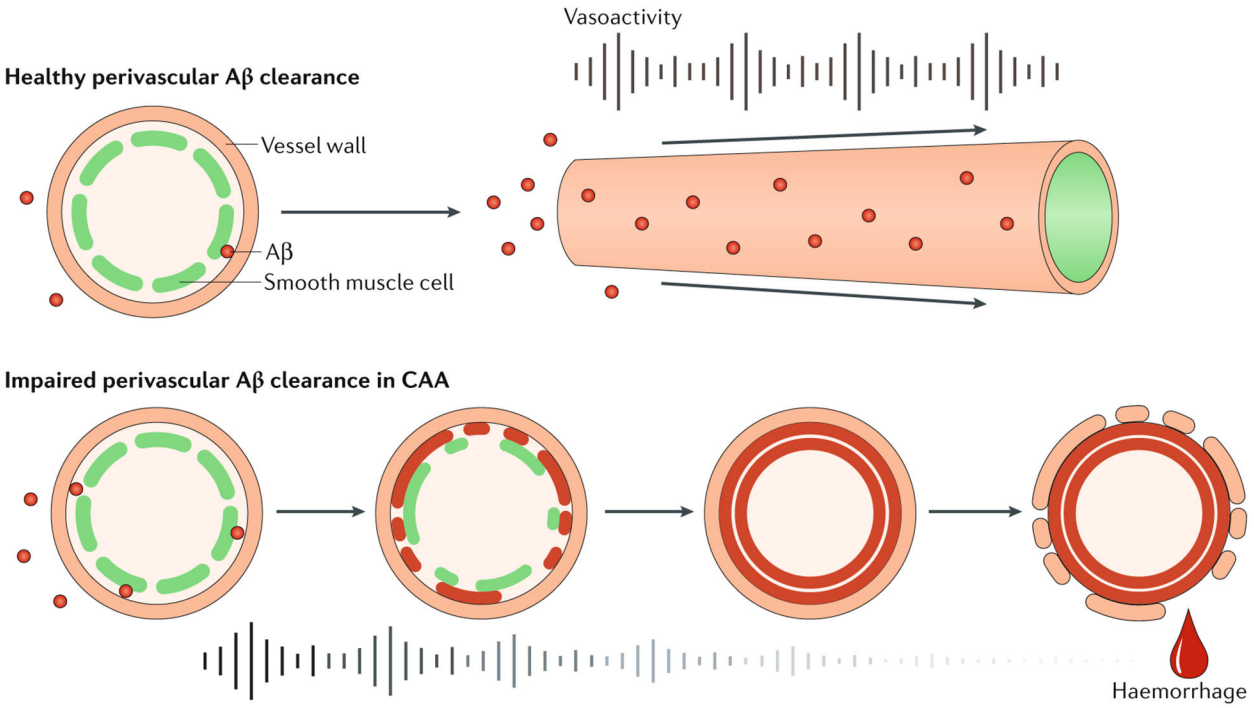

Figure 2 |.

Impairment of perivascular drainage in cerebral amyloid angiopathy and Alzheimer disease. Healthy perivascular amyloid-β (Aβ) clearance occurs along the walls of arteries and relies on intact vessels and normal vasoactivity (top). Interference of perivascular clearance by cerebral amyloid angiopathy (CAA) could establish a self-reinforcing cycle of Aβ deposition, loss of vascular smooth muscle cells and vasoactivity, and further reduction in clearance (bottom). This self-reinforcing mechanism would exacerbate both Alzheimer disease pathology by reducing Aβ clearance and CAA-related vascular lesions, such as haemorrhages, and tissue injury.

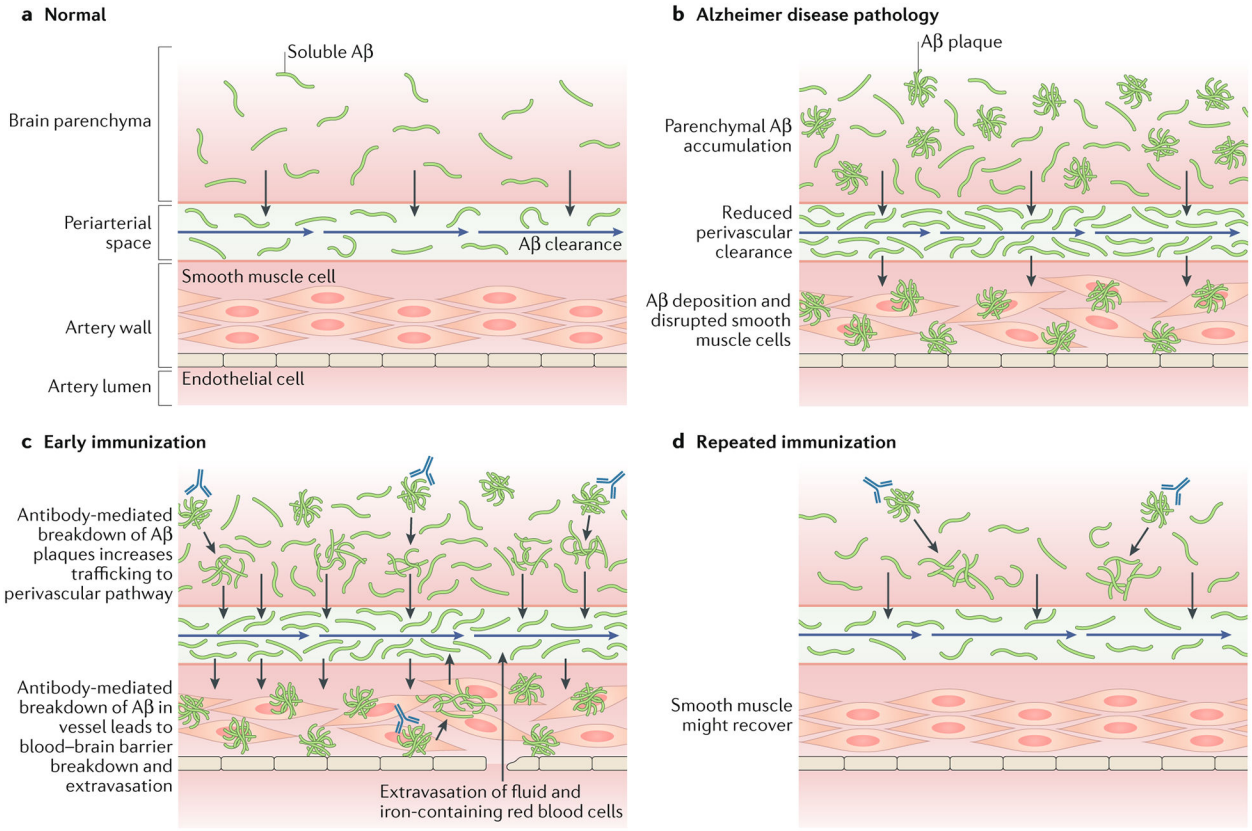

Figure 3 |.

Mechanisms of amyloid-related imaging abnormalities. **a** | In the normal physiological state, amyloid-β (Aβ) is cleared from the brain in part via perivascular pathways. **b** | In Alzheimer disease, accumulation of Aβ in brain parenchyma and vessels results in disrupted vascular integrity and impaired clearance. **c** | Anti-Aβ immunotherapy mobilizes parenchymal Aβ, which moves into already impaired perivascular drainage pathways, and initiates an immune response to vessels. These effects worsen cerebral amyloid angiopathy and render vessels transiently leaky to proteinaceous fluid and blood products, leading to amyloid-related imaging abnormalities (ARIA; ARIA-E and ARIA-H, respectively). d | Limited evidence suggests that with repeated immunization and continued clearance of vascular Aβ, the structural integrity of vessels and the efficiency of perivascular clearance can improve and the risk of ARIA consequently decreases.

Table 1 |

Features associated with vascular or plaque amyloid-β deposition.

Feature	Primarily associated with vascular Aβ deposition	Primarily associated with plaque Aβ deposition	Associated with vascular and plaque Aβ deposition	Refs
Aβ subtype	$Aβ_{40}$, $Aβ_{36}$, $Aβ_{37}$, $Aβ_{38}$, $Aβ_{39}$, $Aβ_{41}$, N3pE-$Aβ_{40}$	$Aβ_{42}$, $Aβ_{43}$, N3pE-$Aβ_{42(43)}$	N/A	86–90
				88, 97
Genetic alterations	*APP* missense mutations within the Aβ sequence	*APP* missense mutations that increase $Aβ_{42}$:$Aβ_{40}$ ratio	*APP* missense mutations within the Aβ sequence	27,100–105
	(Dutch (Glu693Gln), Italian	(London (Val717Ile)	(Arctic (Glu693Gly), Flemish	218,219
	(Glu693Lys), Iowa	*PSEN1* missense mutations	(Ala692Gly))	121,123,220, 221
	(Asp693Asn), Piedmont	(generally before codon 200)	*APP* missense mutations that increase Aβ production without increasing $Aβ_{42}$:$Aβ_{40}$ ratio	125–127
	(Leu705Val))		(Swedish (Lys-Met670-671Asn-Leu)	
			APP duplication or trisomy 21	
			PSEN1 missense mutations	
			(generally after codon 200, including Leu282Val, Leu286Pro	
***APOE* allele**	*APOE**ε2 (CAA-associated haemorrhagic phenotype)	N/A	*APOE**ε4	155,156222,223
Co-deposited proteins (selected[a])	Fibrinogen	Heparan sulfate proteoglycans	Apolipoprotein E	141,150–152
	Matrix metalloproteainase 9	Syndecan-1 and syndecan-3	Apolipoprotein J (clusterin)	141,150,170, 171,181
	Metalloproteinase inhibitor 3)	Heat shock proteins Hsp20 and HspB8	Apolipoprotein A-I	140,145
	Norrin	α1-antichymotrypsin	Complement proteins C1q, C3c, C4d, C5–9	133,141,144
	Collagen-α-2(VI) chain	α 2-macroglobulin)	Vitronectin	150,170
	Sushi repeat-containing protein 1	Intercellular adhesion molecule 1)	Serum amyloid P component	135,182
		Collagenous Alzheimer amyloid plaque component precursor)	Glypican-1	134,224,225
			Syndecan-2	226–228136,141137,141,141,229142,143184,185181,230
			Agrin	182
			Collagen XVIII	183

Feature	Primarily associated with vascular Aβ deposition	Primarily associated with plaque Aβ deposition	Associated with vascular and plaque Aβ deposition	Refs
			Heat shock protein HspB2	

[a]Limited to proteins that co-deposit with Aβ and have been investigated in human brain vascular and parenchymal Aβ deposits. Aβ, amyloid-β; CAA, cerebral amyloid angiopathy; N3pE, pyroglutamate-modified at Glu-3.