Progression of Cerebral Amyloid Angiopathy: A Pathophysiologic Framework

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Summary

Cerebrovascular deposition of amyloid β-peptide (cerebral amyloid angiopathy, CAA) is a common age-related small vessel pathology associated with intracerebral haemorrhage and cognitive impairment. Based on complementary lines of evidence from *in vivo* studies of individuals with hereditary, sporadic, and iatrogenic forms of CAA, histopathologic analyses of affected brains, and experimental studies in transgenic mouse models, we present a framework and timeline for CAA progression from subclinical pathology to clinically manifest disease. Key stages that appear to evolve sequentially over a two-to-three decade timeline are 1) initial vascular amyloid deposition, 2) alteration of cerebrovascular physiology, 3) non-haemorrhagic brain injury, and 4) appearance of haemorrhagic brain lesions. This timeline of steps and the mechanistic processes that link them have substantial implications for identifying the types and timing of candidate disease-modifying interventions for CAA as well as potentially for other cerebral small vessel diseases.

Introduction

CAA is defined by deposition of the amyloid β-peptide (Aβ; noting that this discussion does not pertain to the rare non-Aβ forms of cerebrovascular amyloid) in the walls of small arteries, arterioles, and capillaries of the leptomeninges and cerebral/cerebellar cortex. As a pathology, CAA is common at advanced ages, appearing at a moderate-to-severe grade in nearly one-quarter of autopsied brains obtained from the general population (mean age 84.9 years).[1] CAA emerged as a clinical entity with its identification as a major cause of spontaneous lobar intracerebral haemorrhage (ICH) and has now been linked to lobar ICH across multiple hospital-based patient samples.[1,2] CAA-related lobar ICH carries high morbidity and mortality[3] and recurs at an annual incidence of approximately 7.4%,[4] higher than almost any other identified stroke subtype. CAA-related haemorrhages can also occur in the subarachnoid space overlying brain convexities (designated as convexity subarachnoid haemorrhage [cSAH] when acute or cortical superficial siderosis [cSS] when chronic), where they can present clinically with transient focal neurologic episodes.[5]

Another recently identified clinical manifestation of CAA pathology is its independent contribution to age-related cognitive impairment. Moderate-to-severe CAA at autopsy is associated with more rapid late-life cognitive decline among community-dwelling individuals in analysis controlling for accompanying Alzheimer disease (AD) pathology and other neurodegenerative and vascular pathologies.[6] The mechanism for CAA-related cognitive decline has not been precisely identified, but appears most closely associated with non-haemorrhagic forms of brain injury such as microinfarcts[7] and white matter ultrastructural changes.[8-10]

Determining the sequence and timeline of mechanistic steps linking initial cerebrovascular amyloid deposition to non-haemorrhagic and haemorrhagic brain injury is fundamental to identifying candidate disease-modifying approaches and designing treatment trials. Neuropathological studies are cross-sectional rather than longitudinal, however, limiting their ability to elucidate sequence, timing, and causation. A powerful complementary approach is to monitor mechanistic steps using informative biomarkers in individuals diagnosed with CAA

during life. CAA can be diagnosed in living individuals by their characteristic haemorrhagic lesions according to clinical-radiologic criteria such as the pathologically validated MRI-based Boston[11] or CT-based Edinburgh[12] criteria. Another method for *in vivo* diagnosis is by genetic identification of hereditary forms of CAA such as Dutch-type CAA (D-CAA; see Panel).). [13,14]Studies in living subjects diagnosed during life with sporadic or hereditary CAA have identified aspects of the disease not observable at autopsy such as impaired cerebrovascular reactivity to visual stimulation.[15,16] Longitudinal analysis of hereditary CAA mutation carriers further offers the unique opportunity for mapping the timeline of disease progression prior to appearance of first symptoms or brain lesions.

We sought to create an accurate pathophysiologic framework and timeline for understanding the progression of CAA from the earliest vascular changes to the symptomatic stages of non-haemorrhagic and haemorrhagic brain injury. We took a data-driven approach to creating this framework, drawing on data from neuropathological analyses, *in vivo* biomarker studies of sporadic and hereditary CAA, animal model studies, and recently identified instances of early-onset iatrogenic CAA following presumed childhood exposure to Aβ.[17] Each of these data sources comes with potential limitations to their interpretation, such as differences between animal model and human disease, differences between the clinical courses and comorbidities of hereditary and sporadic CAA,[13] and the imperfect relationship between biomarker measurements and the underlying pathophysiologic steps that they mark. The proposed pathophysiologic framework nonetheless establishes a foundation for designing further biomarker and interventional trials for CAA, for understanding amyloid clearance and deposition in the related condition of AD,[18] and for approaching non-amyloid-related cerebral small vessel diseases.[19]

Panel: Dutch-type CAA (D-CAA)

D-CAA (also referred to as Hereditary Cerebral Haemorrhage with Amyloidosis Dutch-type, HCHWA-D) is the most widely identified and best characterized form of hereditary CAA. It is transmitted via an E693Q substitution in the Amyloid Precursor Protein (APP) as an autosomal

dominant and fully penetrant form of CAA. First lobar ICH in D-CAA mutation carriers occurs at a mean age of approximately 54 with annual recurrence of greater than 20%.[13] The vascular histopathology of D-CAA closely resembles that of sporadic CAA, whereas cardinal features of AD pathology such as dense-core plaques and neurofibrillary tangles are scarce,.[14] making it an essential pure form of CAA.

Search strategy and data plotting methods

Literature used for this paper was found through searches of PubMed between 2002 and December 2022 using the string "cerebral amyloid angiopathy"[MeSH Terms] OR ("cerebral"[All Fields] AND "amyloid"[All Fields] AND "angiopathy"[All Fields]) OR "HCHWA-D"[All Fields], which identified 3129 distinct publications . There were no language restrictions. The final reference list (including additional references prior to 2002 selected from the reference lists of the initially identified publications) was generated based on relevance to the pathophysiologic progression and underlying histopathology of CAA.

Pathophysiologic Framework for CAA Progression

Converging lines of investigation support a sequential pathway for CAA progression consisting of four broad stages: 1) cerebrovascular amyloid deposition, 2) alteration of cerebrovascular physiology, 3) non-haemorrhagic brain injury, and 4) haemorrhagic brain lesions. The steps in this pathwaycorrespond with CSF and neuroimaging biomarkers measured during life in carriers of the D-CAA mutation (Figs. 1 and 2) and with histopathologic changes in CAA-affected vessels at autopsy (Fig. 3). The discussion of the individual steps presented below draws substantially on *in vivo* biomarker data from D-CAA mutation carriers, with additional consideration of biomarker data from individuals diagnosed with sporadic or iatrogenic CAA, histopathologic analysis of brain tissue from hereditary, sporadic, and iatrogenic CAA patients, and analysis of transgenic mouse models of aspects of CAA pathophysiology.

Stage 1: Cerebrovascular amyloid deposition

Vascular amyloid deposition appears to be the earliest mechanistic step detectable in D-CAA mutation carriers. The precise triggers for initial vascular amyloid deposition have not been identified, though characteristics of the Aβ peptide as well as age and other cofactors such as Apolipoprotein E (APOE) genotype appear to play important roles (reviewed in[18]). There is no evidence for substantial Aβ overproduction in sporadic or Dutch-type hereditary CAA,[23] suggesting that Aβ deposition may instead reflect increased aggregation or impaired clearance. The D-CAA APP E693Q substitution appears to increase the mutant peptide's tendency to aggregate and deposit in the vascular wall, particularly the Dutch Aβ40 species.[24]

Vascular amyloid deposition can be inferred by reductions in concentration of Aβ species in CSF,[25] which have been shown to correlate inversely with neuropathologically measured neuritic plaques (which are largely absent in D-CAA, particularly younger mutation carriers) and CAA. Abnormally low concentrations of Aβ42 and Aβ40 have been consistently reported in sporadic CAA[26] and in both the presymptomatic and symptomatic stages of D-CAA.[20,23,27] Decreases in both Aβ species are detectable in D-CAA mutation carriers in their mid-20s, close to 30 years prior to the average age of symptomatic ICH in this population, and then further decrease as the carriers move closer to the age of ICH (Fig. 1). Indeed no study to date has reported an age at which CSF Aβ concentrations are normal in mutation carriers, precluding a determination of the precise age at which CSF Aβ reductions begin. Plasma Aβ, determined by Simoa assay in a subset of somewhat older (mean age 44.1) presymptomatic D-CAA mutation carriers, also showed decreased Aβ40 and Aβ42 concentrations with further reductions in longitudinal follow-up.[23] The reduction in CSF of both the aggregation-prone Aβ42 peptide and the less aggregation-prone Aβ40 peptide in D-CAA differs from the pattern in sporadic AD or ADAD, which are characterized by reduced Aβ42 out of proportion to Aβ40.[20,28] The absolute concentrations of Aβ40 and Aβ42 in D-CAA also appear lower than those observed in ADAD at similar presymptomatic or symptomatic disease stages.[20] More recent work suggests that CSF concentrations of other Aβ species, including Aβ37, 38, and 43 are also abnormally low in presymptomatic and symptomatic D-CAA.[29]

Amyloid-PET imaging with Pittsburgh compound B (PiB) also indicates amyloid deposition in presymptomatic D-CAA, though changes are detectable at later ages than the reductions in CSF Aβ. Analysis of 13 presymptomatic (mean age 45) and 6 symptomatic D-CAA mutation carriers (mean age 55) demonstrated increased PiB retention in the frontolateral temporal/parietal-retrosplenial region of interest also characteristic of PiB retention in AD.[20] Elevated PiB retention in the presymptomatic subset progressively increased over longitudinal scans and with increasing subject age (Fig. 2A). Greater PiB signal correlated with lower CSF Aβ40 concentrations (Pearson correlation coefficient=-0.55 among mutation carriers), supporting the interpretation that both phenomena serve as measures of vascular amyloid deposition. Amyloid imaging with PiB appears less sensitive for detection of D-CAA than ADAD pathology, however, as ADAD mutation carriers demonstrated substantially greater PiB retention at lesser degrees of CSF Aβ reduction. A recent PET-pathological correlation study raised the broader possibility that PiB-PET may be substantially less sensitive for sporadic CAA than AD pathology as well.[30] Reduced sensitivity of PiB for vascular amyloid, whether D-CAA in particular or all forms of CAA, could plausibly account for a later age of first detection among the presymptomatic carriers, who nonetheless demonstrate increased retention approximately 5-10 years prior to first ICH.[20]

A distinct line of evidence for the timeline from first amyloid deposition to symptomatic ICH comes from studies of early-onset CAA apparently triggered iatrogenically by childhood exposure to exogenous Aβ. Previous studies in transgenic animal models had demonstrated that CAA could be generated by intracerebral or intraperitoneal injection of Aβ-containing brain tissue.[31,32] A series of reports since 2015 has identified this phenomenon in humans, with transmission from sources of human tissue including growth hormone preparations, cadaveric dura, and neurosurgical instrumentation, and age of first ICH typically in the third to fifth decades.[17,33,34] These iatrogenic cases of CAA, though infrequent, raise a range of challenging mechanistic issues including the suggestion of prion-like behavior of amyloid fibrils. their apparent predilection for vascular deposition regardless of the pathological source or “strain”

of Aβ (CAA, AD, or both)[35], and the role of additional factors such as neurosurgery or traumatic brain injury.[36] For the purposes of understanding the pathogenesis of CAA, the long latency from amyloid exposure to first symptoms is particularly notable: The mean interval from exposure to exogenous human tissue to clinical symptoms among 23 published cases was 34 years (range 25-46 years).[37] It is difficult to draw direct comparisons between the underlying processes involved in exposure to exogenous wild-type Aβ and endogenous Dutch-type Aβ. The broad timeframe of multiple intervening decades between the presumed date of initial vascular deposition and first ICH, however, appears to be comparable for these two different mechanisms for triggering early-onset CAA.

Histopathologic samples from presymptomatic D-CAA mutation carriers demonstrating the earliest stages of vascular amyloid deposition are generally not available. Neuropathological observations in autopsied brains across various ages and severities of sporadic CAA suggest that Aβ is initially deposited within the outer basement membranes surrounding intact smooth muscle cells, sparing the basement membranes of the endothelium (Fig. 3, stage 1).[38] The surrounded smooth muscle cells at this earliest stage may appear normal or locally atrophic, but are still preserved. A subset of brains with neuropathologic evidence of CAA also demonstrate prominent Aβ deposition in the basement membrane of cortical capillaries, often extending into the surrounding brain parenchyma (termed dyshoric CAA).[39] This distinct capillary phenotype of vascular Aβ deposition appears to correlate more closely than arteriolar-dominant CAA with AD pathology[40] and might thus be more directly related to AD plaque formation.

The anatomic appearance of early CAA formation can be modeled longitudinally by *in vivo* imaging of transgenic mouse models of cerebral amyloidosis such as APPswe/PS1dE9 and Tg2576 mice. These mice demonstrate gradual accumulation of vascular Aβ starting at the larger pial surface arterioles that follows the banding pattern of vascular smooth muscle cells, eventually reaching a confluent circumferential appearance.[41,42] Kinetic modeling of vascular Aβ progression in serially imaged transgenic mice suggests that total growth along the vasculature

occurs primarily via propagation of existing deposits rather than initiation of new vascular Aβ foci.[42] Vascular accumulation of Aβ might be potentiated by the APOE ε4 allele.[43]

Stage 2: Alterations in vascular physiology

Impaired cerebrovascular reactivity, measured in humans by transcranial Doppler or blood-oxygen-level dependent functional MRI (BOLD fMRI) response to visual stimulation, has been identified as a robust feature of sporadic CAA.[15,44,45] BOLD fMRI studies in presymptomatic and symptomatic D-CAA mutation carriers have identified similar alterations in reactivity to visual stimulation, most notably reduced BOLD response amplitude and delayed time to peak response.[16] The finding of impaired vascular reactivity in presymptomatic D-CAA mutation carriers indicate that this is an early manifestation of CAA and can occur in the absence of any MRI-detectable structural brain injury. Based on modeling of available data on the ages of the D-CAA mutation carriers, differences between D-CAA carriers and non-carriers in BOLD fMRI response to visual stimulation appear in the late 30s, with a 1 standard deviation difference between carriers and non-carriers evident 20 years prior to the mean age of first symptomatic ICH (Fig. 1). Follow-up BOLD fMRI in 10 presymptomatic mutation carriers after an approximately 4-year interval demonstrated further decrease in amplitude and increase in time-to-peak of the BOLD response,[46] indicating further progression with advancing disease. Progressive worsening of vascular reactivity over longitudinal BOLD fMRI studies has also been identified in symptomatic sporadic CAA patients.[45]

Histopathologic samples from presymptomatic D-CAA mutation carriers with impaired vascular reactivity are also generally unavailable. Based on mouse models of CAA, impaired vascular physiology appears to correspond to loss of smooth muscle cells in arterioles with circumferential Aβ deposition (Fig. 3, stage 2). In Tg2576 transgenic mice, impaired vascular reactivity to physiological and pharmacological stimuli at 19 months was associated with widespread and severe Aβ deposition in the walls of pial surface arterioles, whereas 8-month mice with no vascular Aβ deposition demonstrated intact vascular physiology.[47] More recent studies using APPswe/PS1dE9 transgenic mice demonstrated impaired evoked vascular

reactivity to a visual stimulation paradigm similar to that used in human BOLD fMRI.[48] The reduction in vascular reactivity in these mice appeared to correlate more closely to loss of vascular smooth muscle cells than CAA burden, suggesting that CAA-related loss of vascular smooth muscle may be the direct mechanism for alterations in cerebrovascular physiology.

CAA-related impairment in vascular physiology may be a contributing mechanism for both non-haemorrhagic brain tissue injury (see following section) and reduced perivascular clearance of the brain's interstitial fluid. Effects of CAA on interstitial fluid clearance are suggested by studies of transgenic mice showing reduced clearance of fluorescent tracers introduced in the brain via injection[49-51] or leakage from neighboring laser-ablated vessels.[48] When analyzed in awake mice, the reduction of perivascular contrast clearance correlated with CAA-related impairment in vascular reactivity at the level of individual vessel segments,[48] supporting a direct causal relationship. These findings are consistent with mathematical models indicating that vasomotion, defined by low frequency arteriolar dilations produced by the contractions of smooth muscle cells, could generate the force required for effective clearance of interstitial fluid.[52,53] If CAA-related alterations in vessel physiology indeed slow brain clearance of soluble extracellular Aβ via the perivascular pathway, it could create a self-reinforcing loop promoting further Aβ deposition in both brain vessels (as CAA) and parenchyma (as the senile plaques characteristic of AD).[18]

Stage 3: Non-haemorrhagic brain tissue injury

Advanced CAA is associated with focal tissue damage and microstructural changes that are distinct from CAA-related haemorrhagic brain lesions. Among the non-haemorrhagic MRI findings linked (at varying degrees of specificity) with sporadic CAA are lobar lacunes, microinfarcts, WMH, visible perivascular spaces in the centrum semiovale (CSO-PVS), and diffusion tensor imaging (DTI) ultrastructural markers such as increased mean diffusivity (MD), decreased fractional anisotropy (FA), and widened PSMD.[7-10,54,55] Changes in PSMD and other DTI-based metrics correlate with cognitive performance (particularly in areas such as executive function and processing speed) in sporadic CAA patients,[8-10] indicating that these markers may

subsume the cumulative clinical impact of widely distributed CAA-related brain injuries on brain network function.

Analysis of white matter MRI changes in D-CAA suggests appearance of non-haemorrhagic brain injury beginning approximately 10-15 years prior to the mean age of symptomatic haemorrhage and rapidly increasing over time (Figs. 1, 2B).[21,56] The onset of these non-haemorrhagic changes is substantially later in D-CAA than abnormalities in CSF Aβ or BOLD fMRI-based vascular reactivity. The time sequence of vascular dysfunction preceding evidence of non-haemorrhagic brain injury is consistent with findings from a mediation analysis in sporadic CAA patients indicating that the association between amyloid-PET signal and WMH volume is mediated by changes in BOLD fMRI response.[55] It is unclear if the observed white matter changes in D-CAA mutation carriers affect cognition as prominent cognitive impairment prior to first ICH has not been identified, though only small numbers of presymptomatic mutation carriers have been tested, mostly at younger ages.[56]

The neuropathologic basis of DTI abnormalities in sporadic CAA has been examined by correlation of *ex vivo* DTI parameters with histopathology. Loss of FA in two white matter tracts (inferior longitudinal fasciculus and anterior thalamic radiation) from 9 sporadic CAA brains was associated with tissue rarefaction and reduced axonal density, and increased MD was associated with reduced myelin density.[57] Microinfarcts detected in regions of the inferior longitudinal fasciculus were also associated with reduced FA and increased MD in these regions. Analysis of the vascular basis of microinfarcts in CAA suggests that these lesions, which appear preferentially in vascular border zone territories of the brain,[58,59] may be caused by hypoperfusion. Among 12 sporadic CAA brains that underwent *ex vivo* MRI-guided histopathologic analysis, microinfarcts tended to occur in areas of severe CAA pathology and increased numbers of Aβ-positive vessels (Fig. 3, stage 3).[59] On serial sectioning, individual vessels at the core of microinfarcts had marked wall thickening, severe circumferential Aβ deposition, and almost complete loss of vascular smooth muscle cells, suggesting focally absent vascular reactivity.

An additional non-haemorrhagic MRI marker associated with sporadic and hereditary CAA is high CSO-PVS count.[60,61] Because of the relative specificity for advanced CAA of a high CSO-PVS category (defined as >20 visible lesions on a single axial MRI slice of one hemisphere[62]), this marker has been incorporated as one of the imaging features of probable CAA in the most recent version (2.0) of the Boston diagnostic criteria.[11] Increased CSO-PVS counts were identified in symptomatic but not presymptomatic D-CAA,[56] suggesting that visible enlargement of the CSO-PVS occurs relatively late in the disease's progression. Histopathologic analysis of individual vessels in brains with sporadic CAA found most enlarged CSO-PVS to be surrounding penetrating arterioles in the white matter that extend from overlying cortical vessels with extensive Aβ deposition and smooth muscle cell loss,[63] consistent with the correlation identified in sporadic CAA patients between CSO-PVS count and amyloid burden on PiB-PET.[64,65] The observed proximity of enlarged CSO-PVS to overlying CAA in individual arterioles[63] raises the intriguing possibility that perivascular space enlargement may be a direct result of CAA-related impairment in perivascular fluid clearance.

Stage 4: Haemorrhagic brain lesions

The most widely recognized clinical manifestations of sporadic and hereditary CAA is ICH, appearing as macrobleeds typically >1 cm in diameter[66] centered in lobar and superficial cerebellar cortex.[67] Widespread use of blood-sensitive T2*-weighted MRI methods has identified several other haemorrhagic manifestations of sporadic and hereditary CAA: cerebral microbleeds, cSS, and cSAH. CAA-related microbleeds typically appear as small round haemorrhagic lesions[68] located in the same lobar and superficial cerebellar brain regions.[11,69] cSS appears as chronic blood products in the cerebral and cerebellar sulci,[70,71] likely representing the evolution of prior cSAH over cortical and cerebellar convexities.

The interrelationship between CAA-related ICH, microbleeds and cSAH/cSS is complex, as individual CAA patients can demonstrate phenotypes that appear predisposed to one of these haemorrhage subtypes in preference to others.[66] Evidence from D-CAA suggests, however, that

all haemorrhagic lesion types emerge roughly concurrently during a distinct haemorrhagic phase of the disease's progression, occurring subsequent to vascular amyloid deposition, altered vascular physiology, and non-haemorrhagic brain injury (Fig. 2C). In D-CAA carriers, microbleeds and cSS are first detected at approximately the same age as first ICH[56] and at least a decade after the earliest evidence of CAA-related non-haemorrhagic imaging changes in white matter (Fig. 1).[21] The model that haemorrhage occurs only late in the course of CAA is consistent with the observation in the general elderly population that the prevalence of moderate-to-severe sporadic CAA pathology (pooled estimate 23.0%) substantially exceeds those of strictly lobar cerebral microbleeds (7.1%) or cSS (0.8%).[1] Similarly, post-mortem brains with sporadic CAA demonstrate approximately 7-fold more microinfarcts than microbleeds[59,72] noting the caveat that all prevalence data are cross-sectional rather than longitudinal. The haemorrhage-prone APP23 transgenic mouse line also demonstrates a substantial time lag between vascular Aβ deposition (readily detectable in 12-month old mice) and appearance of multiple cerebral microbleeds (16 to 20 months).[73,74]

The vascular pathology underlying CAA-related microbleeds has been examined by *ex vivo* MRI-guided histopathological analysis of individual microbleeds and their culprit vessels.[59] Across 12 CAA brains studied, those with the highest total microbleed counts (>80) had worse overall CAA severity than those with lower microbleed counts. At the level of the individual lesions, however, CAA severity was reduced in close proximity to microbleeds—rather than increased, as observed surrounding individual microinfarcts. This apparently paradoxical finding was explained by the observation of individual vessels at the core of microbleeds with smooth muscle cell loss, replacement of the vessel wall with extravasated fibrin, and a paucity of vascular Aβ, a distinct constellation of changes termed vascular remodeling (Fig. 3, stage 4). These remodeling changes did not appear to represent a consequence of haemorrhage as they could also be observed in a subset of vessels without associated microbleeds, suggesting that they may instead be causative of bleeding. Further histopathologic analysis of affected vessels in seven CAA brains identified markedly increased reactive astrocyte and activated microglia staining immediately surrounding remodeled vessels,[75] raising the important possibility that

inflammation may be a contributing mechanism to the vascular changes most closely linked to haemorrhage. Other evidence regarding the mechanisms underlying vascular remodeling comes from earlier studies demonstrating association between the APOE ε2 allele and CAA-related vasculopathic changes such as concentric vessel splitting and fibrinoid necrosis.[43]

The requirement for amyloid-laden vessels to undergo a distinctremodeling step to produce haemorrhage offers a plausible explanation for haemorrhagic lesions appearing later than non-haemorrhagic lesions in CAA's disease course. We note that vascular remodeling is not a feature exclusive to CAA, as severe arteriolosclerosis for example is also associated with changes such as fibrinoid necrosis.[76]

Histopathologic identification of individual culprit vessels for cSS is more challenging because of the diffuse extension of these leptomeningeal haemorrhages. An analysis of histologic sections containing cSS identified Iron-positive hemosiderin in the subarachnoid space and underlying cortex, reactive astrocytes, activated microglia, and increased CAA severity in leptomeningeal vessels, with particularly prominent concentric splitting of the vessel wall, another form of vascular remodeling.[77] Further evidence for the importance of vessel remodeling in cSS formation is its observed association with APOE ε2.[78]

Timeline for CAA Progression

Biomarker data from D-CAA mutation carriers create a broad timeline for the steps in D-CAA progression as plotted in Fig. 1. These studies suggest amyloid deposition (based on reduced CSF Aβ) 20-30 years prior to first ICH, followed by measurable alterations in vascular physiology approximately 20 years prior to first ICH and appearance of non-haemorrhagic MRI injury approximately 10 years prior to first ICH.

In interpreting this proposed timeline, we note several important limitations. One is that observable biomarkers are likely to be an imperfect measure of the underlying phenomenon that they are meant to reflect. This is particularly evident for PiB-PET retention in D-CAA, which

based on its relatively modest signal compared to concurrent reductions of CSF Aβ[20] may be insensitive to the early vascular deposition of Aβ carrying the Dutch substitution or to vascular Aβ in general.[30] A second notable limitation is that findings from D-CAA may not be fully generalizable to the more common condition of sporadic CAA. D-CAA appears to have more aggressive progression of its haemorrhagic stage,[13] potentially foreshortening the period of non-haemorrhagic brain injury, as well as a relative paucity of AD pathology.[14] Determining the effects of each of these factors on the timeline of disease progression represents a key area for ongoing investigation. It is somewhat reassuring in this regard that iatrogenic CAA—another condition with clear differences from the sporadic or hereditary disease—shows a roughly similar three-decade timeline from exposure to abnormal amyloid to first ICH.[37]

These caveats noted, the biomarker changes plotted in Fig. 1 represents a data-driven timeline for D-CAA—and potentially sporadic CAA—progression. Current data suggest that CSF Aβ,[27] vascular physiology,[45] and non-haemorrhagic brain injury markers[9] continue progression through the presymptomatic and symptomatic disease phases without definite plateau (though not necessarily in a linear manner as depicted in the figure). Haemorrhagic lesions also continue to accumulate during the symptomatic disease phase, but we have chosen to depict haemorrhage in this timeline as the average age of first ICH because of the sudden jump in morbidity and mortality associated with this event.[13]

The other major clinical manifestation of CAA is cognitive impairment. Available pre-ICH cognitive testing data from D-CAA mutation carriers (tested at relatively young ages, approximately 20 years prior to first expected ICH) has not identified substantial decline.[46,56] In sporadic CAA, conversely, cognitive impairment is often a primary clinical manifestation even in the absence of ICH.[79] Teasing apart the relative contributions to cognitive impairment from the overlapping pathologic injuries in CAA brains (including concomitant AD pathology, largely absent in D-CAA[14]) is complex. The preponderance of evidence, however, demonstrates the closest correlations of sporadic CAA cognitive performance with non-haemorrhagic white matter biomarkers such as the diffusion tensor-based PSMD or global efficiency metrics [8-10]

characteristic of Stage 3. Cognitive decline can be additionally punctuated by acute lobar ICH.[80] However the other features of CAA stage 4 such as appearance of cerebral microbleeds, while necessary for MRI diagnosis of probable CAA,[11] have not consistently demonstrated correlation with cognitive performance.[79,81]

Comparison of presymptomatic biomarker studies in hereditary CAA versus ADAD suggests a longer presymptomatic timeline for CAA than AD. Divergence between ADAD mutation carriers and non-carriers of CSF Aβ and brain glucose metabolism appears on the order of 15-20 years before the predicted onset of dementia,[22,82] approximately a decade closer to disease onset than the earliest changes in D-CAA. This apparent difference could indicate that CAA-related vessel remodeling and ICH require longer periods to result from amyloid deposition than AD-related neuronal and synaptic loss, but this interpretation remains speculative.

Conclusions and Future Directions

The proposed pathophysiologic framework for CAA progression (Fig. 4) broadens the question of identifying disease-modifying treatment from *what* (i.e. what interventions might be effective*?*) to also include *when* (i.e. when in the disease course will the interventions be applied?). Haemorrhagic brain lesions, required for imaging-based diagnosis of probable CAA,[11] appear to occur only late in the disease course. Treatment of individuals diagnosed by detection of CAA-related bleeds might therefore need to focus on late steps in disease progression such as vessel remodeling and activation of astrocytes and microglia.[75] Treatment strategies aimed at lowering of Aβ production or vascular deposition, conversely, might be more appropriate for earlier stages of CAA progression, highlighting the importance of developing diagnostic methods less dependent on haemorrhagic lesions. It is also notable, that the pre-haemorrhage disease stages of vascular amyloid deposition, impaired vascular physiology, and non-haemorrhagic brain injury continue to progress through the symptomatic period, raising the possibility that these processes may continue to contribute to clinical disease progression even after onset of first haemorrhage. The decades-long interval over which CAA progresses to first haemorrhage indicates an extended time window in which Aβ lowering

treatments could be initiated, provided that sufficiently specific diagnostic methods can be identified for this pre-haemorrhage period.

Basing treatment strategies on this proposed framework requires that the identified steps are not just markers but causative mechanisms for CAA progression. Although temporal sequence does not establish causation, there are plausible mechanisms linking the outlined processes. Vascular Aβ deposition is spatially linked to the loss of vascular smooth muscle cells[75] that appear responsible for impaired physiologic reactivity,[48] and to ischemic brain injury in the form of microinfarcts.[59] Loss of normal elements in the vessel wall, while not necessarily a cause of subsequent haemorrhage, appears to be a prerequisite for the additional remodeling steps such as fibrin extravasation into the vessel wall.[59,75] The potential for impaired vascular reactivity to reduce Aβ clearance from the brain[48] adds the further mechanistic possibility of a feedback loop that potentiates further Aβ deposition. Maintenance or restoration of normal vascular physiology, conversely, would be predicted to slow further accumulation of Aβ and progression of underlying CAA—and potentially AD—pathology.[18]

Various aspects of this mechanistic chain—including those with major implications for identifying candidate treatments for CAA—remain incompletely understood and important targets for future research. These include the determinants of the initial vascular Aβ deposits that appear to serve as seeds for further CAA growth,[42] the precise steps in vessel remodeling that are responsible for symptomatic ICH,[75] and the physiologic mechanisms that produce the range of CAA-related non-haemorrhagic brain injuries. The mechanisms linking small vessel structural and functional changes to non-haemorrhagic brain injury may be particularly complex. Candidate mechanisms derived from various small vessel disease experimental systems include ischemia due to lost blood flow at strategic sites within the small vessel network,[83] blood-brain barrier leakage,[84] and increased small vessel pulsatility.[85,86] Another intriguing question is the precise determinant of ICH occurrence, as age of first ICH varies substantially even among individuals carrying identical D-CAA mutations.[13]

While the framework described here derives from studies of hereditary and sporadic CAA, many of the pathological and physiological processes are shared with arteriolosclerosis, the other common age-related cerebral small vessel disease.[87] Like CAA, cerebral arteriolosclerosis is associated with pathological replacement of normal cellular elements of the tunica media with hyaline material,[76] impaired vascular reactivity to physiologic stimulation,[88,89] and both non-haemorrhagic and haemorrhagic brain injury.[76] The lipohyalinosis/fibrinoid necrosis pathologic changes linked to arteriolosclerosis-related haemorrhage involve infiltration of fibrin into the vessel wall, notably reminiscent of CAA-related vascular remodeling,[59,75] suggesting potential shared mechanisms at the time of bleeding. Future analysis of the timeline for progression of arteriolosclerosis will determine how these postulated disease stages might affect this small vessel disease's response to interventions, with intriguing evidence that intensive blood pressure lowering may modify small vessel dysfunction even late in the disease course.[90,91]

Authors' contributions

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Declaration of interests

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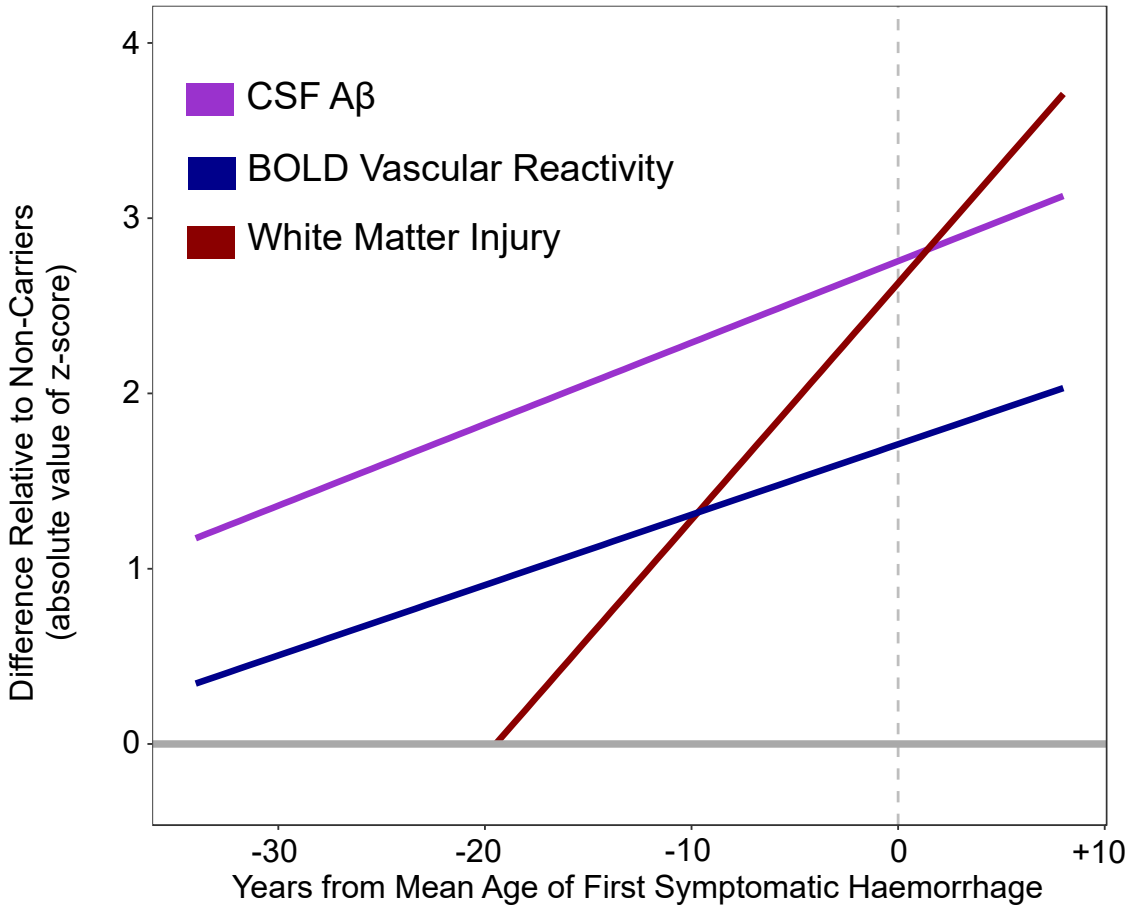


Figure 1. Biomarker progression in Dutch-type hereditary cerebral amyloid angiopathy (D-CAA) Divergence in key biomarkers between D-CAA mutation carriers and non-carriers was estimated from individual-level data of published studies on D-CAA CSF Aβ[20], cerebrovascular reactivity,[16] and white matter injury[21] obtained from the authors. [16,20,21]To allow for comparison across measures with differing scales and variabilities, differences between D-CAA carriers and non-carriers were calculated and standardized based on the standard deviation of each biomarker measure in D-CAA non-carriers, an approach similar to biomarker studies of autosomal dominant AD (ADAD).[22] The resulting z-scored difference scores were then plotted against subject age (in years), labeling year 0 as the mean age of first symptomatic ICH (age 54) in D-CAA carriers.[13] CSF Aβ was plotted as the averaged z-scores of CSF Aβ40 and Aβ42. White

matter injury was plotted as the averaged z-scores of white matter T2-weighted hyperintensity (WMH) volume, white matter T1-weighted hypointensity volume, and histogram peak of skeletonized white matter mean diffusivity (PSMD) as described.[21]

Figure 2. Examples of neuroimaging biomarker progression in carriers of the Dutch-type hereditary cerebral amyloid angiopathy (D-CAA) mutation (A). Amyloid deposition detected by positron emission tomography using 11C-Pittsburgh Compound B (PiB) in three asymptomatic D-CAA carriers. Tracer retention, calculated as standardized uptake value ratio (SUVr) in frontal, lateral temporal/parietal, and retrosplenial cortex using cerebellar gray matter as reference, increased with subject age.[20] (B) Progression of non-haemorrhagic brain injury in an asymptomatic D-CAA mutation carrier. Longitudinal MRI T2-weighted FLAIR images obtained four years apart demonstrate increased volume of white matter hyperintensity (WMH). (C) Emergence of a first symptomatic intracerebral haemorrhage (seen on CT scan and MRI susceptibility weighted imaging [SWI]) in the setting of prior non-haemorrhagic brain injury (WMH seen on FLAIR images) and microbleeds (on SWI) in a D-CAA mutation carrier.

Figure 2A

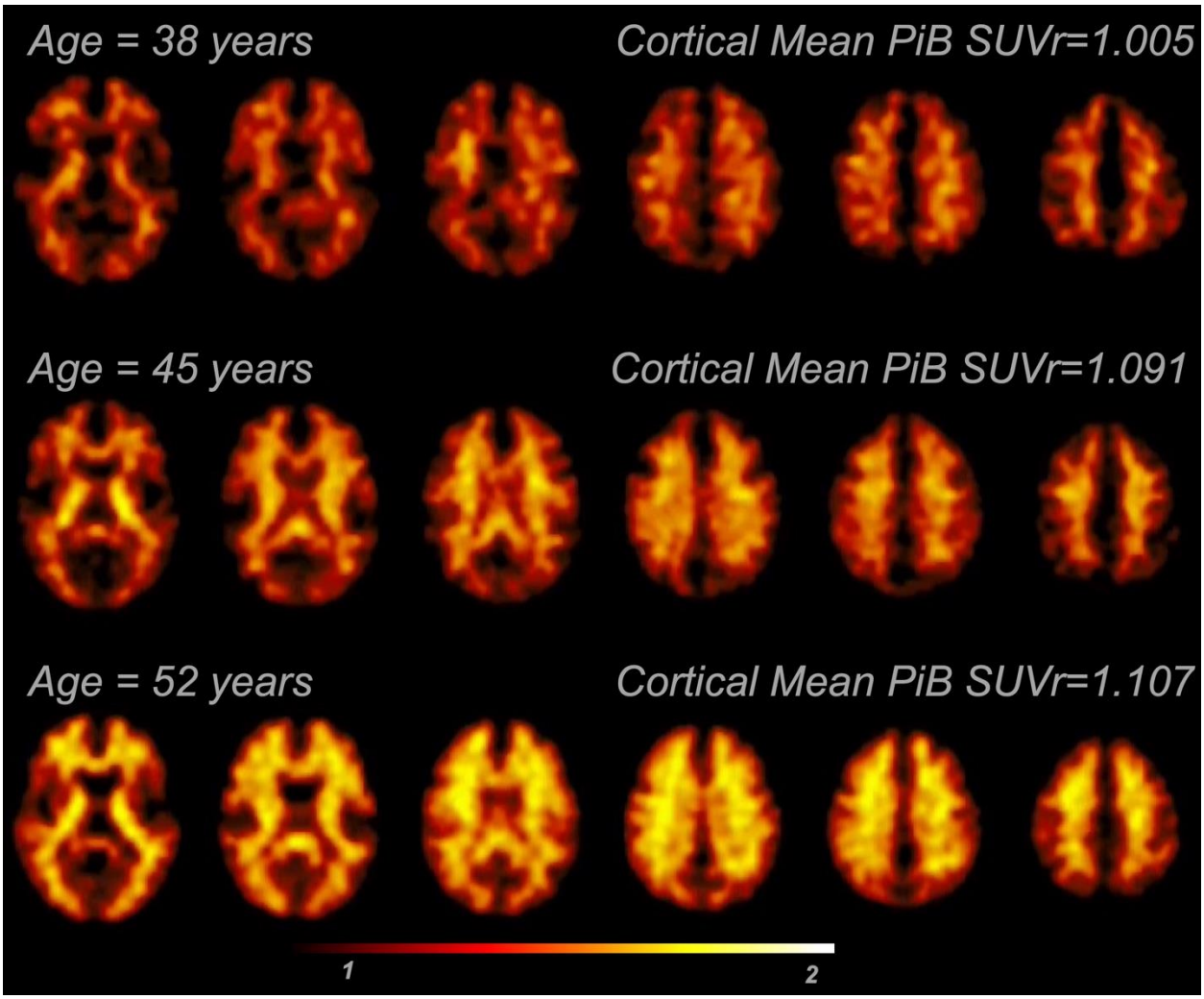

Age = 38 years
Cortical Mean PiB SUVr=1.005
Age = 45 years
Cortical Mean PiB SUVr=1.091
Age = 52 years
Cortical Mean PiB SUVr=1.107
1
2

Figure 2B

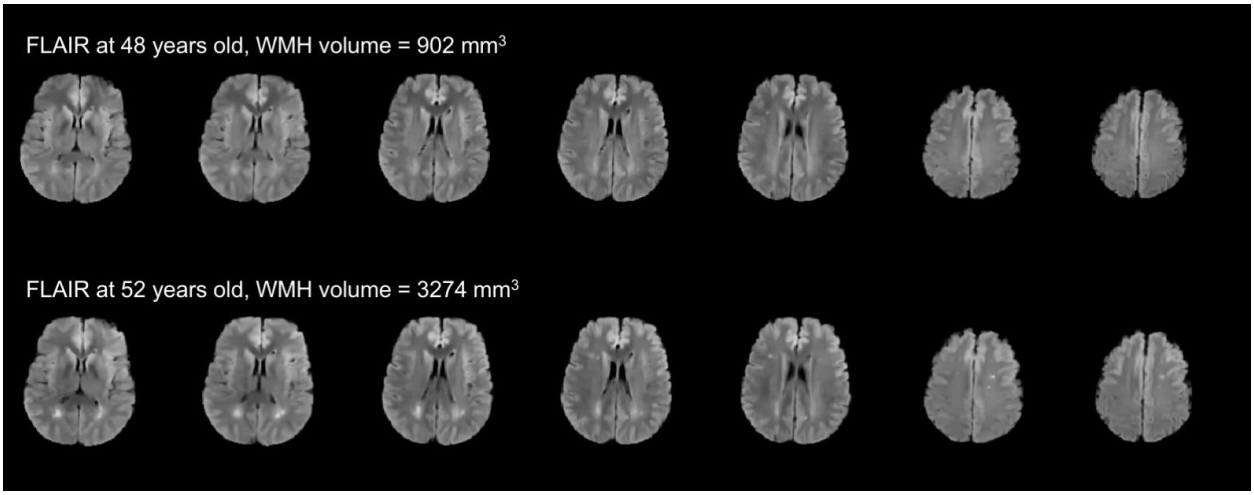
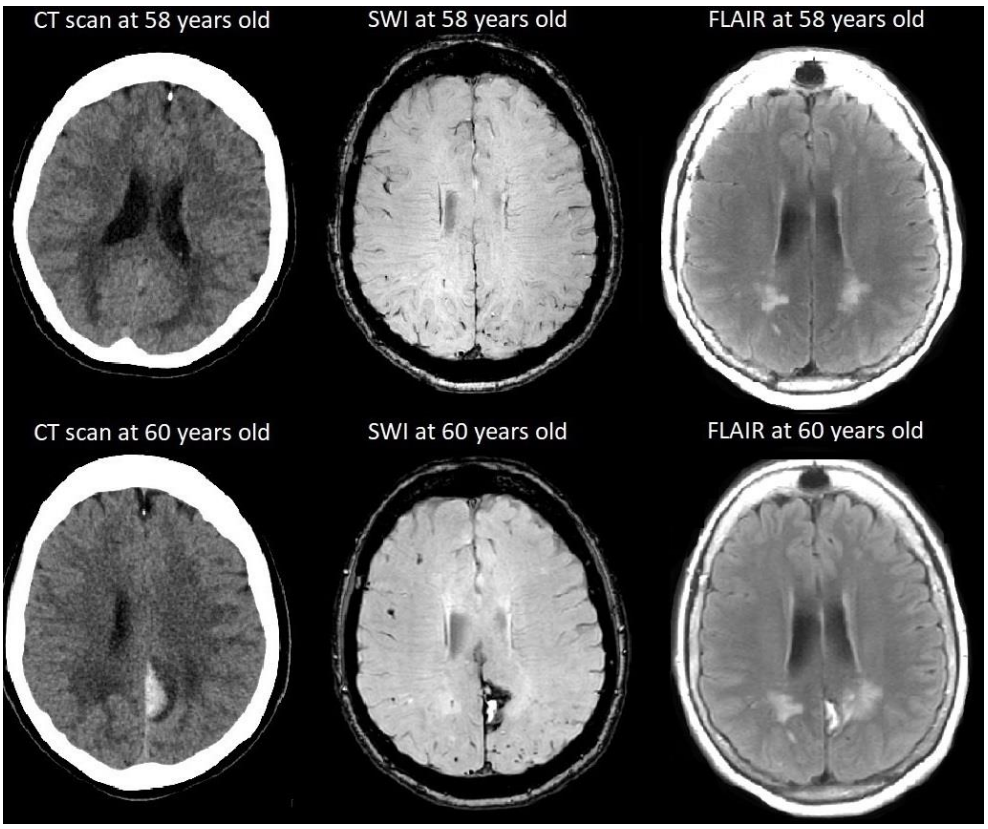

FLAIR at 48 years old, WMH volume = 902 mm3
FLAIR at 52 years old, WMH volume = 3274 mm3

Figure 2C


CT scan at 58 years old
SWI at 58 years old
FLAIR at 58 years old
CT scan at 60 years old
SWI at 60 years old
FLAIR at 60 years old

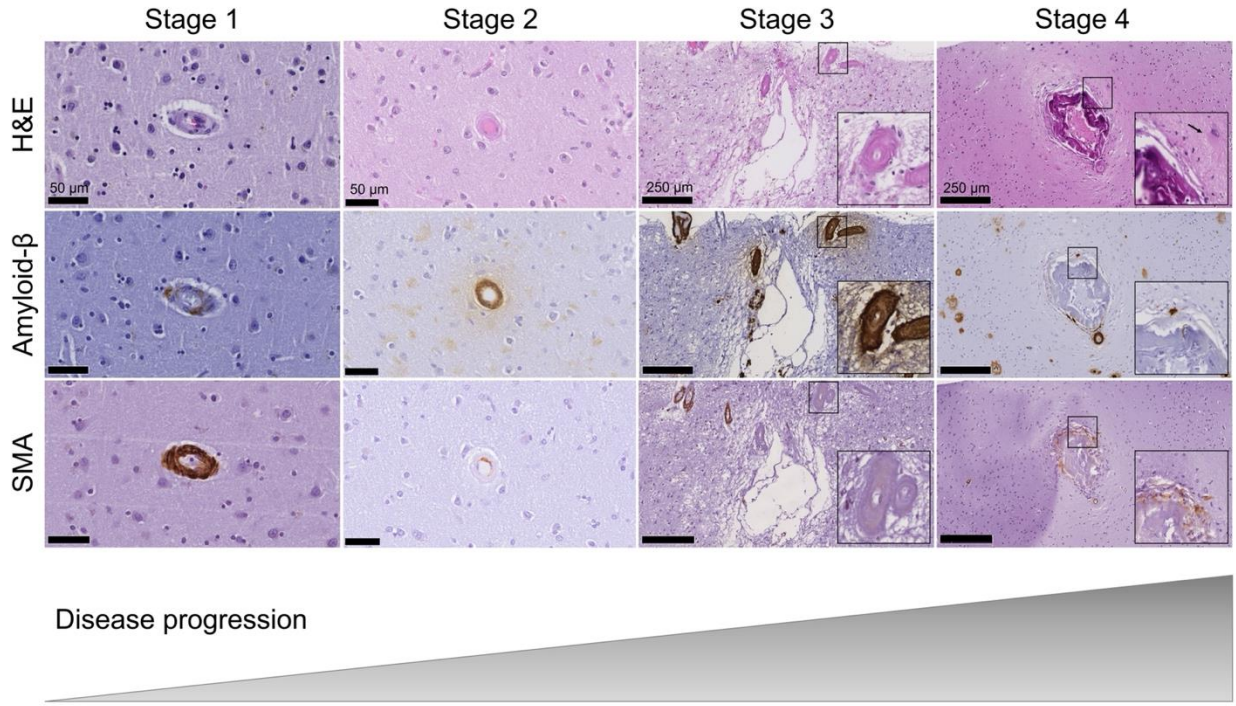


Figure 3. Underlying vascular pathologies associated with stages of cerebral amyloid angiopathy progression. Stage 1 is characterized by initial amyloid-β (Aβ) deposition in otherwise intact arterioles (corresponding to Vonsattel scale[75,92] grade I). In Stage 2, vascular Aβ has become circumferential, resulting in complete replacement of vascular smooth muscle cells (Vonsattel grade II). Stage 3 is characterized by non-haemorrhagic forms of brain injury; the panels show a cortical microinfarct surrounding an arteriole with circumferential Aβ deposition and complete loss of smooth muscle cells (Vonsattel grade II). Stage 4 is characterized by vascular remodeling and haemorrhagic lesions; the panels show a remodeled blood vessel with vessel wall fragmentation (Vonsattel grades III-IV), loss of both smooth muscle cells and Aβ, and associated activated astrocytes (arrow on H&E panel). Scale bars in the two columns on the left are 50 µm; scale bars in the two columns on the right are 250 µm. H&E: hematoxylin & eosin, SMA: smooth muscle actin.

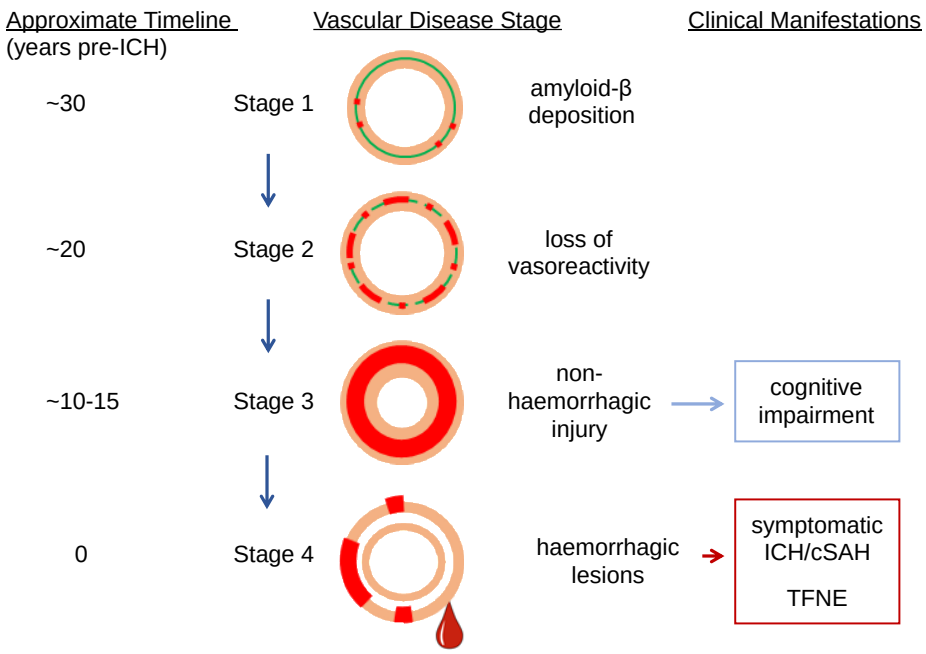


Figure 4. Schematic of cerebral amyloid angiopathy (CAA) progression. The numbers under Timeline are approximate years prior to average age of first symptomatic haemorrhage at which each disease stage is detectable (derived from Dutch-type hereditary CAA; see Fig. 1). The vessels drawn under Vascular Disease Stage depict progressive vascular deposition of amyloid (red) and loss of vascular smooth muscle cells (green) at advancing stages of pathological severity, altered physiology, and non-haemorrhagic and haemorrhagic brain injuries. The corresponding Clinical Manifestations represent the most common presentations of symptomatic CAA. As shown in the figure, symptomatic haemorrhagic lesions occur in a subset of CAA patients with non-haemorrhagic brain injuries. ICH: intracerebral haemorrhage, cSAH: convexity subarachnoid haemorrhage, TFNE: transient focal neurologic episodes.