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Cerebral amyloid angiopathy, which is defined by cerebrovascular deposition of amyloid β, 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 cerebral amyloid angiopathy, histopathological analyses of affected brains, and experimental studies in transgenic mouse models, we present a framework and timeline for the progression of cerebral amyloid angiopathy from subclinical pathology to the clinical manifestation of the disease. Key stages that appear to evolve sequentially over two to three decades are (stage one) initial vascular amyloid deposition, (stage two) alteration of cerebrovascular physiology, (stage three) non-haemorrhagic brain injury, and (stage four) appearance of haemorrhagic brain lesions. This timeline of stages and the mechanistic processes that link them have substantial implications for identifying disease-modifying interventions for cerebral amyloid angiopathy and potentially for other cerebral small vessel diseases.

Introduction

Cerebral amyloid angiopathy is defined by the deposition of amyloid β (Aβ) in the walls of small arteries, arterioles, and capillaries of the leptomeninges, cerebral cortex, and cerebellar cortex. As a pathology, cerebral amyloid angiopathy is common at advanced ages, appearing at a moderate-to-severe grade in nearly a quarter of autopsied brains from the general population (mean age 84·9 years).[1] Cerebral amyloid angiopathy emerged as a clinical entity after its identification as a major cause of spontaneous lobar intracerebral haemorrhage, and has now been linked to lobar intracerebral haemorrhage in many hospital-based cohorts.[1,2] Cerebral amyloid angiopathy-related lobar intracerebral haemorrhage carries high morbidity and mortality,[3] and recurs at an annual incidence of approximately 7·4%,[4] which is higher than the annual incidence of almost any other stroke type. In these patients, haemorrhages can also occur in the subarachnoid space overlying brain convexities (designated as convexity subarachnoid haemorrhage if acute, or cortical superficial siderosis when chronic), that can present clinically with transient focal neurological episodes.[5]

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

Establishing the sequence and timeline of the mechanistic steps linking initial cerebrovascular amyloid deposition to non-haemorrhagic and haemorrhagic brain injury is fundamental to identify disease-modifying approaches and to design treatment trials. However, neuropathological studies are cross-sectional rather than longitudinal, which limits their ability to elucidate sequence, timing, and causation. A powerful complementary approach is to monitor mechanistic steps using informative biomarkers in individuals with cerebral amyloid angiopathy. Cerebral amyloid angiopathy can be diagnosed by its characteristic haemorrhagic lesions according to clinical-radiological 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, such as the Dutch-type cerebral amyloid angiopathy (panel).[13,14] Studies in patients diagnosed with sporadic or hereditary cerebral amyloid angiopathy have identified aspects of the disease that are not observable at autopsy, such as impaired cerebrovascular reactivity to visual stimulation.[15,16] Longitudinal evaluation of carriers of hereditary mutations further allows for mapping the

Panel: Dutch-type cerebral amyloid angiopathy

Dutch-type cerebral amyloid angiopathy (also referred to as hereditary cerebral haemorrhage with amyloidosis of the Dutch type) is the most widely identified and best characterised form of hereditary cerebral amyloid angiopathy. It is transmitted via an E693Q subsitution in the APP protein. The first lobar intracerebral haemorrhage in carriers of the mutation occurs at a mean age of approximately 54 years, with an annual recurrence higher than 20%.[13] The vascular histopathology of Dutch-type cerebral amyloid angiopathy closely resembles that of sporadic cerebral amyloid angiopathy, whereas cardinal features of Alzheimer's disease pathology, such as dense-core plaques and neurofibrillary tangles, are scarce,[14] making it an essentially pure form of cerebral amyloid angiopathy.

timeline of disease progression before the appearance of first brain lesions and symptoms.

We sought to create a pathophysiological framework and timeline for the progression of cerebral amyloid angiopathy, from the earliest vascular changes to the symptomatic stages of non-haemorrhagic and haemorrhagic brain injury. This framework does not pertain to the rare non-Aβ forms of cerebrovascular amyloid angiopathy. We took a data-driven approach, drawing on data from neuropathological analyses, in vivo biomarker studies of sporadic and hereditary cerebral amyloid angiopathy, animal model studies, and findings since 2015 of early-onset iatrogenic cerebral amyloid angiopathy after 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 cerebral amyloid angiopathy,[13] and the imperfect relationship between biomarker measurements and the underlying pathophysiology. The proposed pathophysiological framework nonetheless establishes a foundation for designing further biomarker and interventional trials for cerebral amyloid angiopathy, for understanding amyloid clearance and deposition in Alzheimer's disease,[18] and for addressing non-amyloid-related cerebral small vessel diseases.[19]

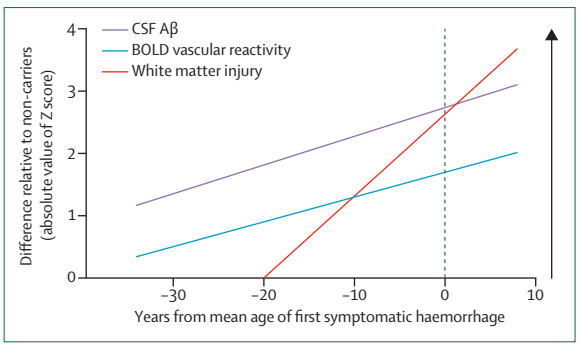


Figure 1: **Biomarker progression in Dutch-type hereditary cerebral amyloid angiopathy**
Divergence in key biomarkers between carriers and non-carriers of the Dutch-type cerebral amyloid angiopathy mutation was estimated from individual-level data of published studies. Amyloid β in CSF,[20] cerebrovascular reactivity,[16] and white matter injury[21] data were obtained from the authors.[16,20,21] To allow for comparison across measures with differing scales and variabilities, differences between carriers and non-carriers were calculated and standardised based on the SD of each biomarker measure in non-carriers, an approach similar to that of biomarker studies of autosomal dominant Alzheimer's disease.[22] The resulting z-scored difference scores were then plotted against age (in years), labelling year 0 as the mean age (54 years) of first symptomatic intracerebral haemorrhage in carriers of the mutation.[13] Data on amyloid β in CSF were plotted as the averaged z-scores of the two isoforms Aβ40 and Aβ42. Data on cerebrovascular reactivity were plotted as the amplitude of the blood-oxygen-level-dependent response to visual stimulation.[16] White matter injury was plotted as the averaged z-scores of white matter T2-weighted hyperintensity volume, white matter T1-weighted hypo-intensity volume, and histogram peak of skeletonised white matter mean diffusivity, as described.[21] Aβ=amyloid β.

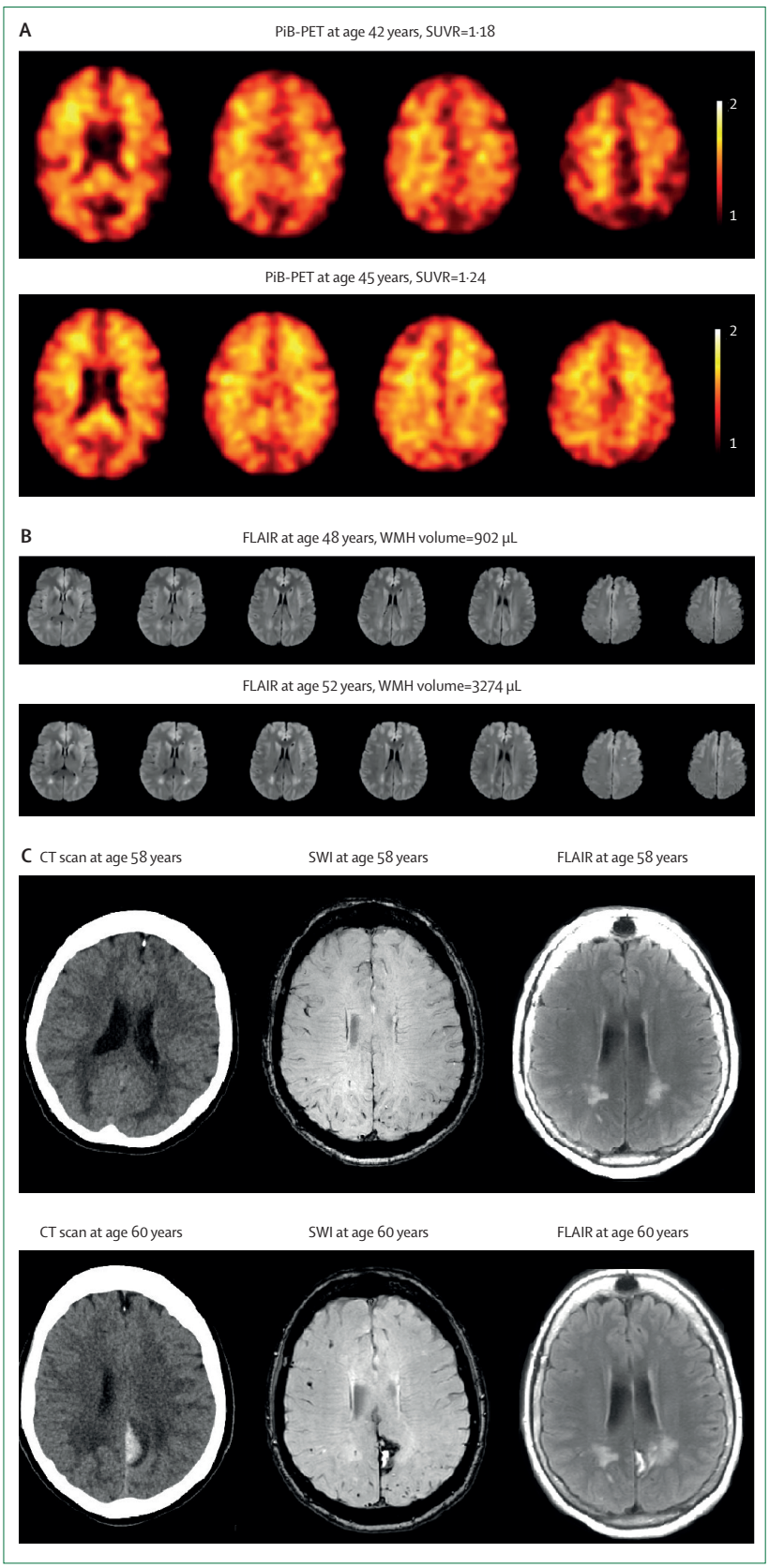
Pathophysiological framework

Converging lines of investigation support a sequential pathway for the progression of cerebral amyloid angiopathy that consists of four broad stages: (1) cerebrovascular amyloid deposition, (2) alteration of cerebrovascular physiology, (3) non-haemorrhagic brain injury, and (4) haemorrhagic brain lesions. Each stage draws on in vivo biomarker data from carriers of the Dutch-type cerebral amyloid angiopathy mutation (figure 1),[20–22] with additional consideration of biomarker data from individuals with sporadic or iatrogenic cerebral amyloid angiopathy, histopathological analysis of brain tissue from patients with hereditary or sporadic cerebral amyloid angiopathy, and findings from transgenic mouse models of aspects of cerebral amyloid angiopathy pathophysiology.

Stage one: cerebrovascular amyloid deposition

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

Vascular amyloid deposition in the brain can be inferred by reductions in the concentration of Aβ species in CSF,[25] which have been shown to correlate inversely with neuritic plaques (largely absent in neuropathological analyses of Dutch-type cerebral amyloid angiopathy, particularly in younger carriers of the mutation). Abnormally low concentrations of Aβ42 and Aβ40 in CSF have been consistently reported in patients with sporadic cerebral amyloid angiopathy[26] and in both the presymptomatic and symptomatic stages of Dutch-type cerebral amyloid angiopathy.[20,23,27] Decreases in both Aβ species are detectable in CSF in carriers of the Dutch-type cerebral amyloid angiopathy mutation as young as their mid-20s, approximately 30 years before the mean age of symptomatic intracerebral haemorrhage. Aβ42 and Aβ40 decrease further as carriers get older (figure 1). Indeed, no study to date has reported an age at which CSF Aβ concentrations are normal in mutation carriers, precluding an ascertainment of the precise age at which reductions in the concentrations of CSF Aβ begin. Plasma Aβ, assessed by ultra-sensitive immunoassays in a subset of somewhat older (mean age 44·1 years [SD 4·3]) presymptomatic carriers, also showed decreased Aβ40 and Aβ42 concentrations, with further reductions detected in longitudinal follow-up.[23] The reduction in CSF and plasma of both the aggregation-prone Aβ42 peptide and the less



aggregation-prone Aβ40 peptide in Dutch-type cerebral amyloid angiopathy differs from the pattern in sporadic Alzheimer's disease or autosomal dominant Alzheimer's disease, which are characterised by reduced CSF Aβ42 without major reduction of CSF Aβ40.[20,28] The absolute concentrations of Aβ40 and Aβ42 in CSF in Dutch-type cerebral amyloid angiopathy also appear lower than those in autosomal dominant Alzheimer's disease at both presymptomatic or symptomatic stages.[20] A 2021 study suggests that CSF concentrations of other Aβ species, including Aβ37, Aβ38, and Aβ43, are also abnormally low in presymptomatic and symptomatic carriers of the Dutch-type cerebral amyloid angiopathy mutation.[29]

Amyloid-PET imaging with Pittsburgh compound B also indicates amyloid deposition in presymptomatic carriers, although changes are detectable at later ages than the reductions in CSF Aβ. Analysis of 13 presymptomatic (mean age 45·4 years [SD 5·2]) and six symptomatic carriers (mean age 55·3 years [SD 1·8]) of the Dutch-type cerebral amyloid angiopathy mutation showed increased Pittsburgh compound B retention in the frontal, lateral temporal–parietal, and retrosplenial region of interest, which is also characteristic of Pittsburgh compound B retention in Alzheimer's disease.[20] Elevated Pittsburgh compound B retention in presymptomatic carriers progressively increased over longitudinal scans and with older age (figure 2). Greater Pittsburgh compound B signal was correlated with lower CSF Aβ40 concentrations (r=–0·55 among mutation carriers), supporting the interpretation that both phenomena serve as measures of vascular amyloid deposition. However, amyloid imaging with Pittsburgh compound B appears less sensitive for detection of Dutch-type cerebral amyloid angiopathy than autosomal dominant Alzheimer's disease pathology, because carriers of autosomal dominant Alzheimer's disease mutations showed substantially greater Pittsburgh compound B retention at lesser degrees of CSF Aβ reduction. A 2021 PET pathological correlation study raised the broader possibility that Pittsburgh compound B PET could be substantially less sensitive for sporadic cerebral amyloid angiopathy than for Alzheimer's disease pathology.[30] Reduced sensitivity of Pittsburgh compound B for vascular amyloid, either for Dutch-type cerebral

Figure 2: **Neuroimaging biomarkers progression in carriers of the Dutch-type hereditary cerebral amyloid angiopathy mutation**
(A) 11C-Pittsburgh compound B-PET , for the detection of amyloid β deposition, in four asymptomatic carriers of the Dutch-type cerebral amyloid angiopathy mutation. Tracer retention, calculated as standardised uptake value ratio in frontal, lateral temporal–parietal, and retrosplenial cortex using cerebellar grey matter as reference increased with age.[20] (B) Progression of non-haemorrhagic brain injury in an asymptomatic carrier of the Dutch-type cerebral amyloid angiopathy mutation. Longitudinal MRI T2-weighted FLAIR images obtained 4 years apart show increased volume of white matter hyperintensity. (C) Emergence of a first symptomatic intracerebral haemorrhage (seen on CT scan and MRI SWI) in the setting of previous non-haemorrhagic brain injury (white matter hyoerintensity seen on FLAIR images) and microbleeds (on SWI) in a carrier of the Dutch-type cerebral amyloid angiopathy mutation. FLAIR=fluid attenuated inversion recovery. SWI=susceptibility weighted imaging.

amyloid angiopathy in particular or for all forms of cerebral amyloid angiopathy, could plausibly account for a later age of first detection among the presymptomatic carriers, who nonetheless show increased retention approximately 5–10 years before the first intracerebral haemorrhage.[20]

A distinct line of evidence for the timeline from first amyloid deposition to symptomatic intracerebral haemorrhage comes from studies of early-onset cerebral amyloid angiopathy thought to be triggered iatrogenically by childhood exposure to exogenous Aβ. Previous studies in transgenic animal models showed that cerebral amyloid angiopathy could be generated by intracerebral or intraperitoneal injection of Aβ-containing brain tissue.[31,32] A series of reports since 2015 has identified this effect in humans, with transmission from sources of human tissue including growth hormone preparations, cadaveric dura, and neurosurgical instrumentation, and age of first intracerebral haemorrhage typically in the third to fifth decades of life.[17,33,34] These iatrogenic cases of cerebral amyloid angiopathy, although infrequent, raise a range of challenging mechanistic issues, including the potential prion-like behaviour of amyloid fibrils; the apparent predilection of the exogenous amyloid for vascular deposition regardless of the pathological source or strain of amyloid β (ie, cerebral amyloid angiopathy, Alzheimer's disease, 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 cerebral amyloid angiopathy, 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 case reports was 34 years (range 25–46).[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 timeframe of intervening decades between the presumed date of initial vascular deposition and first intracerebral haemorrhage, however, appears to be similar for these two different mechanisms of triggering early-onset cerebral amyloid angiopathy.

Histopathological samples from presymptomatic carriers of the Dutch-type cerebral amyloid angiopathy mutation at the earliest stages of vascular amyloid deposition are generally not available. Neuropathological observations in autopsied brains across patients of various ages and with different severities of sporadic cerebral amyloid angiopathy suggest that Aβ is initially deposited within the outer basement membranes surrounding smooth muscle cells, sparing the basement membranes of the endothelium.[38] At this earliest stage, the smooth muscle cells can appear normal or locally atrophic, but are still preserved (figure 3).[39] A subset of brains with neuropathological evidence of cerebral amyloid angiopathy also show prominent Aβ deposition in the basement membrane of cortical capillaries, often extending into the surrounding brain parenchyma (termed dyshoric cerebral amyloid angiopathy).[40] This distinct capillary presentation of vascular Aβ deposition appears to correlate more closely with Alzheimer's disease than does arteriolar cerebral amyloid angiopathy,[41] and might thus be more directly related to Alzheimer's disease plaque formation.

The anatomical appearance of early cerebral amyloid angiopathy formation can be modelled longitudinally by in vivo imaging of transgenic mouse models of cerebral amyloidosis, such as APPswe/PS1dE9 and Tg2576 mice. These mice show gradual accumulation of vascular Aβ starting at the larger arterioles of the pial surface that follows the banding pattern of vascular smooth muscle cells, eventually reaching a confluent circumferential appearance.[42,43] Kinetic modelling of vascular Aβ progression in serially imaged transgenic mice suggests that amyloid accumulation along the vasculature occurs primarily via propagation of existing deposits rather than initiation of new vascular Aβ foci.[43] Vascular accumulation of Aβ might be potentiated by the APOE ε4 allele.[44]

Stage two: alterations in vascular physiology

Impaired cerebrovascular reactivity, measured 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 cerebral amyloid angiopathy.[15,45,46] BOLD fMRI studies in presymptomatic and symptomatic carriers of the Dutch-type cerebral amyloid angiopathy mutation have identified similar alterations in reactivity to visual stimulation, most notably reduced BOLD fMRI response amplitude and delayed time to peak response.[16] The finding of impaired vascular reactivity in presymptomatic carriers of the Dutch-type cerebral amyloid angiopathy mutation indicate that impaired vascular reactivity is an early manifestation of cerebral amyloid angiopathy and can occur in the absence of any MRI-detectable structural brain injury. Based on modelling of the ages of carriers, differences between carriers and non-carriers in BOLD fMRI response to visual stimulation appear at approximately ages 34–38 years, with an SD of 1 between carriers and non-carriers evident 20 years before mean age of first symptomatic intracerebral haemorrhage. Follow-up BOLD fMRI in ten presymptomatic carriers after an approximately 4-year interval showed further decrease in amplitude and increase in time-to-peak of the BOLD response,[47] indicating further progression. Progressive worsening of vascular reactivity over longitudinal BOLD fMRI studies has also been identified in symptomatic patients with sporadic cerebral amyloid angiopathy.[46]

Histopathological samples from presymptomatic carriers of the Dutch-type cerebral amyloid angiopathy mutation with impaired vascular reactivity are not generally available. Based on mouse models of cerebral amyloid angiopathy, impaired vascular physiology appears to correspond to the loss of smooth muscle cells in arterioles with circumferential Aβ deposition. In Tg2576 transgenic mice, impaired vascular reactivity to

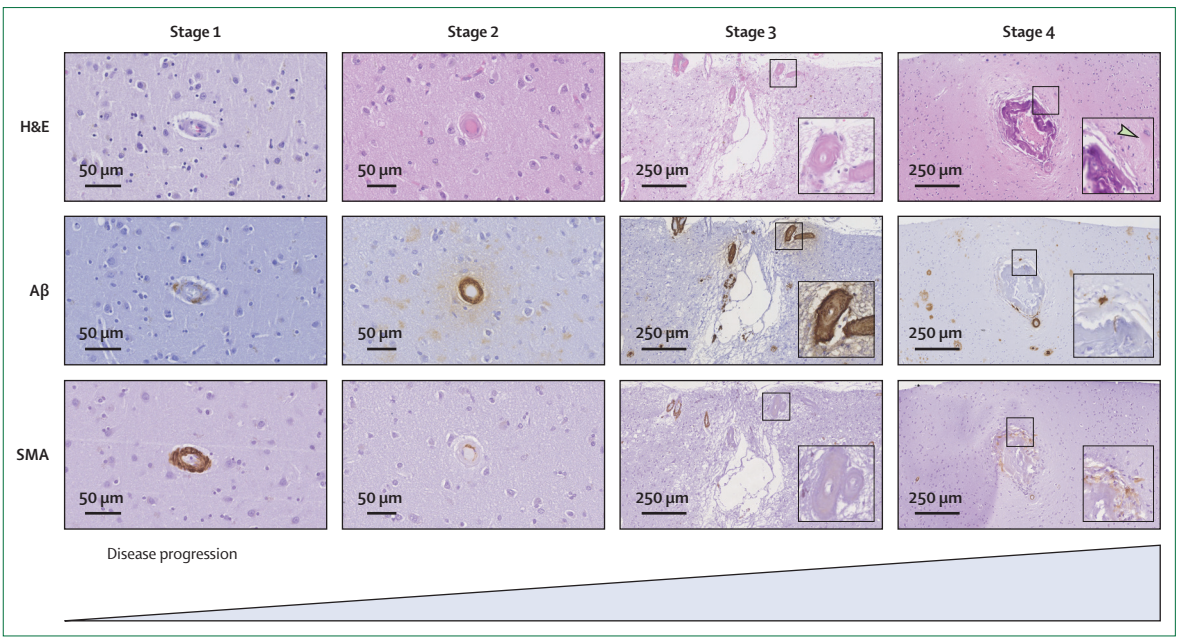


Figure 3: **Underlying vascular pathologies associated with stages of cerebral amyloid angiopathy progression**
(A) Stage one is characterised by initial Aβ deposition in otherwise intact arterioles (corresponding to Vonsattel scale[39] grade 1). (B) In stage two, vascular Aβ has become circumferential, resulting in complete replacement of vascular smooth muscle cells (Vonsattel grade 2). (C) stage three is characterised 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 2). (D) Stage four is characterised by vascular remodelling and haemorrhagic lesions; the panels show a remodeled blood vessel with vessel wall fragmentation (Vonsattel grades 3–4), 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 and scale bars in the two columns on the right are 250 μm. Aβ=amyloid β. H&E=Hematoxylin and Eosin. SMA=smooth muscle actin.

physiological and pharmacological stimuli at age 19 months was associated with widespread and severe Aβ deposition in the walls of pial surface arterioles, whereas mice aged 8 months with no vascular Aβ deposition showed intact vascular physiology.[48] A 2020 study using APPswe/PS1dE9 transgenic mice showed impaired evoked vascular reactivity to a visual stimulation paradigm similar to that used in human BOLD fMRI.[49] The reduction in vascular reactivity in these mice appeared to correlate more closely with the loss of vascular smooth muscle cells than with cerebral amyloid angiopathy burden, suggesting that cerebral amyloid angiopathy-related loss of vascular smooth muscle could be the direct mechanism for alterations in cerebrovascular physiology.

Cerebral amyloid angiopathy-related impairment in vascular physiology might be a contributing mechanism for both non-haemorrhagic injury and reduced perivascular clearance of the brain's interstitial fluid. Effects of cerebral amyloid angiopathy on interstitial fluid clearance are suggested by studies of transgenic mice showing reduced clearance of fluorescent tracers introduced in the brain via injection[50–52] or leakage from neighbouring laser-ablated vessels.[49] When analysed in awake mice, the reduction of perivascular contrast clearance correlated with cerebral amyloid angiopathy-related impairment in vascular reactivity at the scale of individual vessel segments,[49] 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.[53,54] If cerebral amyloid angiopathy-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 cerebral amyloid angiopathy) and parenchyma (as the senile plaques characteristic of Alzheimer's idsease).[18]

Stage three: non-haemorrhagic injury of brain tissue

Advanced cerebral amyloid angiopathy is associated with focal tissue damage and microstructural changes that are distinct from haemorrhagic brain lesions. Among the non-haemorrhagic MRI findings linked (at varying degrees of specificity) with sporadic cerebral amyloid angiopathy are lobar lacunes, microinfarcts, white matter hyperintensities, visible perivascular spaces in the centrum semiovale (CSO-PVS), and diffusion tensor imaging (DTI) ultrastructural markers such as increased mean diffusivity, decreased histogram fractional anisotropy, and widened peak width of skeletonised mean diffusivity (PSMD).[7–10,55,56] Changes in PSMD and other DTI-based metrics correlate with cognitive performance (particularly with executive function and processing speed) in patients with sporadic cerebral amyloid angiopathy,[8–10]

indicating that these markers could subsume the cumulative clinical effect of widely distributed cerebral amyloid angiopathy-related injuries on brain network function.

Analysis of white matter MRI changes in people with Dutch-type cerebral amyloid angiopathy suggests that non-haemorrhagic brain injury begins approximately 10–15 years before the mean age of symptomatic haemorrhage, and rapidly increases over time (figure 2B).[21,57] The onset of these non-haemorrhagic changes occurs substantially later than the onset of abnormalities in CSF Aβ or BOLD fMRI-based vascular reactivity (figure 1). The time sequence of vascular dysfunction preceding non-haemorrhagic brain injury is consistent with findings from a mediation analysis in patients with sporadic cerebral amyloid angiopathy indicating that the association between amyloid-PET signal and white matter hyperintensity volume is mediated by changes in BOLD fMRI response.[56] It is unclear if the observed white matter changes in carriers of the Dutch-type cerebral amyloid angiopathy mutation affect cognition, because cognitive impairment has not been detected before the first intracerebral haemorrhage, although only 12 presymptomatic carriers have been tested at a mean age of 34 years.[57]

The neuropathological basis of DTI abnormalities in patients with sporadic cerebral amyloid angiopathy has been examined by correlation of ex vivo DTI parameters with histopathology. Loss of fractional anisotropy in two white matter tracts (inferior longitudinal fasciculus and anterior thalamic radiation) in the brains of nine patients with sporadic cerebral amyloid angiopathy was associated with tissue rarefaction and reduced axonal density, while increased mean diffusivity was associated with reduced myelin density.[58] Microinfarcts detected in regions of the inferior longitudinal fasciculus were also associated with reduced fractional anisotropy and increased mean diffusivity in these regions. Analysis of the vascular basis of microinfarcts in patients with cerebral amyloid angiopathy suggests that these lesions, which appear preferentially in territories of the vascular border,[59,60] could be caused by hypoperfusion. In ex vivo MRI-guided histopathological analysis of the brains of 12 patients with sporadic cerebral amyloid angiopathy, microinfarcts tended to occur in areas of severe vascular amyloid pathology and increased numbers of Aβ-positive vessels.[60] 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 (figure 3), suggesting that vascular reactivity was absent.

An additional non-haemorrhagic MRI marker associated with sporadic and hereditary cerebral amyloid angiopathy is high CSO-PVS count.[61,62] Because of the relative specificity for advanced cerebral amyloid angiopathy of a high CSO-PVS count (defined as >20 visible lesions on a single axial MRI slice of one hemisphere[63]), this marker has been incorporated as one of the imaging features of probable cerebral amyloid angiopathy in the most recent version of the Boston diagnostic criteria.[11] Increased CSO-PVS counts were identified in symptomatic patients with Dutch-type cerebral amyloid angiopathy but not in presymptomatic carriers,[57] suggesting that visible enlargement of the CSO-PVS occurs relatively late in the disease's progression. Histopathological analysis of vessels in the brains of patients with sporadic cerebral amyloid angiopathy found most enlarged CSO-PVS surrounding penetrating arterioles in the white matter, that extend from overlying cortical vessels with extensive Aβ deposition and smooth muscle cell loss.[64] This finding is consistent with the correlation identified in patients with sporadic cerebral amyloid angiopathy between CSO-PVS count and amyloid burden on Pittsburgh compound B PET.[65,66] The observed proximity of enlarged CSO-PVS to overlying cerebral amyloid angiopathy in arterioles[64] raises the intriguing possibility that perivascular space enlargement could be a direct result of impairment in perivascular fluid clearance.

Stage four: haemorrhagic brain lesions

The most widely recognised clinical manifestations of both sporadic and hereditary cerebral amyloid angiopathy is intracerebral haemorrhage, appearing as macrobleeds typically larger than 1 cm in diameter[67] located in the lobar and superficial cerebellar cortex.[68] T2-weighted MRI methods have identified several other haemorrhagic manifestations of sporadic and hereditary cerebral amyloid angiopathy: cerebral microbleeds, cortical superficial siderosis, and convexity subarachnoid haemorrhage. Microbleeds typically appear as small round haemorrhagic lesions[69] located in the same lobar and superficial cerebellar brain regions.[11,70] Cortical superficial siderosis appears as chronic blood products in the cerebral and cerebellar sulci,[71,72] probably resulting from the evolution of previous subarachnoid haemorrhage over cortical and cerebellar convexities.

The interrelationship between intracerebral haemorrhage, microbleeds, cortical superficial siderosis, and convexity subarachnoid haemorrhage is complex because individual patients with cerebral amyloid angiopathy can appear predisposed to one of these haemorrhagic subtypes over others.[67] Evidence from patients with Dutch-type cerebral amyloid angiopathy suggests, however, that all haemorrhagic lesions emerge roughly concurrently during a distinct haemorrhagic phase of the disease's progression, occurring after vascular amyloid deposition, altered vascular physiology, and non-haemorrhagic brain injury. In carriers of the Dutch-type cerebral amyloid angiopathy mutation, microbleeds and cortical superficial siderosis are first detected at approximately the same age as first intracerebral haemorrhage (mean age 54 years)[13,57] and at least a decade after the earliest evidence of non-haemorrhagic imaging changes in white matter (figures 1, 2C).[21] The hypothesis that haemorrhage

occurs only late in the course of cerebral amyloid angiopathy is consistent with the observation that the prevalence of moderate-to-severe sporadic cerebral amyloid angiopathy pathology in autopsy studies of the general population (pooled estimate 23·0%, mean age 80–85 years) substantially exceeds the prevalence of strictly lobar cerebral microbleeds (7·1%) and cortical superficial siderosis (0·8%).[1] Similarly, in MRI studies of the general population (mean age 65–70 years), microinfarcts are approximately seven times more common than microbleeds,[60,73] noting the caveat that all prevalence data are cross-sectional rather than longitudinal. The haemorrhage-prone APP23 transgenic mice also show a substantial time lag between vascular Aβ deposition (readily detectable in mice aged 12 months) and appearance of multiple cerebral microbleeds (detectable in mice aged 16–20 months).[74,75]

The vascular pathology underlying microbleeds has been examined by ex vivo MRI-guided histopathological analysis.[60] Across the brains of 12 patients with cerebral amyloid angiopathy, those with the highest total microbleed counts (>80) had worse overall severity of cerebral amyloid angiopathy than those with lower microbleed counts (<80). At the scale of the individual lesions, however, severity of cerebral amyloid angiopathy was reduced near microbleeds, a result that contrasts with the previously noted increase in cerebral amyloid angiopathy severity near 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 (figure 3), which are a distinct constellation of changes termed vascular remodelling. These remodelling changes did not appear to be a consequence of haemorrhage, because they could be observed also in a subset of vessels without associated microbleeds, suggesting that vascular remodelling might instead be causative of bleeding. Further histopathological analysis of affected vessels in the brains of seven patients with cerebral amyloid angiopathy identified substantially increased reactive astrocyte and activated microglia staining surrounding remodeled vessels.[76] This finding raises the possibility that inflammation could be a contributing mechanism to the vascular changes most closely linked to haemorrhage. Other evidence regarding the mechanisms underlying vascular remodelling comes from earlier studies demonstrating the association between the APOE ε2 allele and changes such as concentric vessel splitting and fibrinoid necrosis.[44] The requirement for amyloid-laden vessels to undergo a remodelling step to produce haemorrhage offers a plausible explanation for the observation of haemorrhagic lesions appearing later than non-haemorrhagic lesions in the disease course. We note that vascular remodelling is not a feature exclusive to cerebral amyloid angiopathy. In fact, severe arteriolosclerosis is also associated with changes such as fibrinoid necrosis.[77]

The histopathological identification of individual vessels with cortical superficial siderosis is more challenging than identifying the culprit vessel for microbleeds, because of the diffuse extension of these leptomeningeal haemorrhages. An analysis of histological sections identified iron-positive haemosiderin in the subarachnoid space and underlying cortex, reactive astrocytes, activated microglia, and increased severity of cerebral amyloid angiopathy in leptomeningeal vessels, with particularly prominent concentric splitting of the vessel wall, which is another form of vascular remodelling.[78] Further evidence for the importance of vessel remodelling in cortical superficial siderosis is its association with APOE ε2.[79]

Timeline for the progression of cerebral amyloid angiopathy

Biomarker data from carriers of the Dutch-type cerebral amyloid angiopathy mutation can provide a broad timeline for the steps in the disease's progression (figure 2). These studies suggest amyloid deposition (based on reduced CSF Aβ) 20–30 years before first intracerebral haemorrhage, followed by measurable alterations in vascular physiology approximately 20 years before first intracerebral haemorrhage, and appearance of non-haemorrhagic MRI injury approximately 10 years before first intracerebral haemorrhage.

In interpreting this proposed timeline, we note several important limitations. One limitation is that biomarkers are likely to be imperfect measures of the underlying processes that they are meant to reflect. This limitation is particularly evident for Pittsburgh compound B PET retention in Dutch-type cerebral amyloid angiopathy, which—based on its relatively modest signal compared with concurrent reductions of CSF Aβ[20]—might be insensitive to the early vascular deposition of Aβ or to vascular Aβ in general.[30] A second notable limitation is that findings from Dutch-type cerebral amyloid angiopathy might not be fully generalisable to the more common condition of sporadic cerebral amyloid angiopathy. Dutch-type cerebral amyloid angiopathy appears to have a more aggressive progression of its haemorrhagic stage than the sporadic disease,[13] which potentially foreshortens the period of non-haemorrhagic brain injury, and has a relative paucity of Alzheimer's disease pathology.[14] Determining the effects of each of these factors on the timeline of disease progression is a key area of ongoing investigation. It is somewhat reassuring that iatrogenic cerebral amyloid angiopathy—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 intracerebral haemorrhage.[37]

Noting these caveats, the biomarker changes plotted in figure 2 represents a data-driven timeline for Dutch-type cerebral amyloid angiopathy—and potentially for sporadic cerebral amyloid angiopathy—progression. Current data suggest that CSF Aβ,[27] vascular physiology,[46]

and non-haemorrhagic brain injury markers[9] keep progressing through the presymptomatic and symptomatic disease phases without a definite plateau (although not necessarily in a linear manner as depicted in figure 1). Haemorrhagic lesions also continue to accumulate during the symptomatic disease phase, but we have chosen to depict haemorrhage in this timeline as the mean age of first intracerebral haemorrhage because of the sudden rise in morbidity and mortality associated with this event.[13]

The other major clinical manifestation of cerebral amyloid angiopathy is cognitive impairment. Cognitive testing data from carriers of the Dutch-type cerebral amyloid angiopathy mutation (tested at a mean age of 34 years, approximately 20 years before first expected intracerebral haemorrhage) have not identified cognitive decline.[47,57] Conversely, in patients with sporadic cerebral amyloid angiopathy, cognitive impairment is often a primary clinical manifestation even in the absence of intracerebral haemorrhage.[80] Disentangling the relative contributions to cognitive impairment from the overlapping pathological injuries in the brains of patients with cerebral amyloid angiopathy (including concomitant Alzheimer's disease pathology, which is largely absent in Dutch-type cerebral amyloid angiopathy[14]) is complex. The preponderance of evidence, however, shows the closest correlations of cognitive performance in people with sporadic cerebral amyloid angiopathy with non-haemorrhagic white matter biomarkers, such as the diffusion tensor-based PSMD or global efficiency metrics[8–10] characteristic of stage three (ie, non-haemorrhagic brain tissue injury). Cognitive decline can be additionally punctuated by acute lobar intracerebral haemorrhage.[81] However, the other features of stage four of cerebral amyloid angiopathy, such as appearance of cerebral microbleeds, although necessary for MRI diagnosis of probable cerebral amyloid angiopathy,[11] have not consistently shown correlation with cognitive performance.[80,82]

The comparison of presymptomatic biomarker studies in hereditary cerebral amyloid angiopathy and autosomal dominant Alzheimer's disease suggests a longer presymptomatic timeline for cerebral amyloid angiopathy than for Alzheimer's disease. Divergence between carriers and non-carriers of autosomal dominant Alzheimer's disease mutations in CSF Aβ and brain glucose metabolism appears about 15–20 years before the predicted onset of dementia,[22,83] approximately a decade closer to disease onset than the earliest changes in Dutch-type cerebral amyloid angiopathy. This difference could indicate that the appearance of vessel remodelling and intracerebral haemorrhage requires longer periods after amyloid deposition than those needed for neuronal and synaptic loss, but this interpretation remains speculative.

Conclusions and future directions

Our proposed pathophysiological framework for the progression of cerebral amyloid angiopathy (figure 4) broadens the question of identifying disease-modifying treatment from what (ie, what interventions might be effective?) to also include when (ie, when in the disease course will the interventions be applied?). Haemorrhagic brain lesions, required for imaging-based diagnosis of probable cerebral amyloid angiopathy,[11] appear to occur only late in the disease course, decades after first deposition of amyloid in vessels. Treatment of individuals with cerebral amyloid angiopathy-related bleeds might therefore need to focus on late steps in disease progression, such as vessel remodelling and activation of astrocytes and microglia.[76] Treatment strategies aimed at lowering Aβ production or vascular deposition, conversely, might be more appropriate for earlier stages of cerebral amyloid angiopathy, highlighting the importance of developing diagnostic methods that are less dependent on haemorrhagic lesions. It is also notable that the pre-haemorrhagic 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 could continue to contribute to clinical disease progression even after onset of first haemorrhage. The decades-long interval

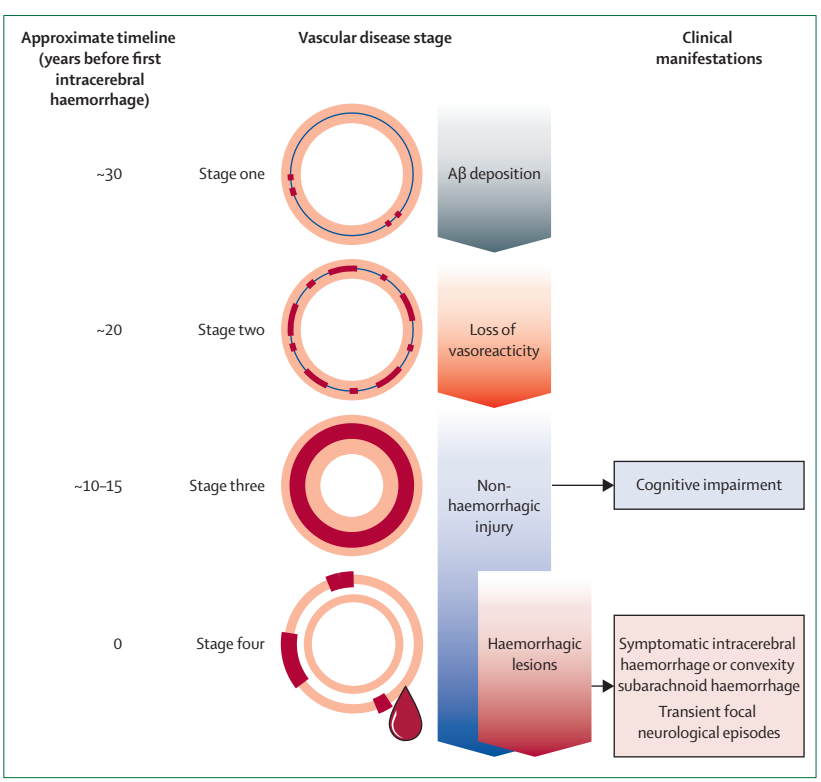


Figure 4: **Schematic of cerebral amyloid angiopathy progression**
Approximate timeline refers to the approximate number of years before mean age of first symptomatic haemorrhage at which each disease stage is detectable (derived from Dutch-type hereditary cerebral amyloid angiopathy; figure 1). Vascular disease stage vessels depict progressive vascular deposition of amyloid (red) and loss of vascular smooth muscle cells (blue) 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 cerebral amyloid angiopathy. Symptomatic haemorrhagic lesions occur in a subset of patients with cerebral amyloid angiopathy with non-haemorrhagic brain injuries.

Search strategy and selection criteria

We selected the literature for this Personal View through searches of PubMed for papers published 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 published before 2002 selected from the reference lists of the initially identified publications) was generated based on their relevance to the pathophysiological progression and underlying histopathology of cerebral amyloid angiopathy.

over which cerebral amyloid angiopathy progresses to first haemorrhage indicates an extended time window in which Aβ-lowering treatments could be initiated, provided that specific diagnostic methods can be developed.

A key question for applying our framework to selection of candidate treatment strategies is whether the identified steps are not just disease markers but mechanisms for the progression of cerebral amyloid angiopathy. Although the temporal sequence does not establish causation, plausible causative mechanisms link the outlined processes. Vascular Aβ deposition is spatially linked to the loss of vascular smooth muscle cells,[76] which appear responsible for impaired physiological reactivity,[49] and to ischaemic brain injury, in the form of microinfarcts.[60] The loss of the normal constituent cells in the vessel wall, although not necessarily a cause of subsequent haemorrhage, appears to be a prerequisite for the additional remodelling steps, such as fibrin extravasation into the vessel wall.[60,76] Impaired vascular reactivity might reduce Aβ clearance from the brain,[49] which adds the further mechanistic possibility of a feedback loop that potentiates Aβ deposition. Maintenance or restoration of vascular physiology, conversely, would be predicted to slow the accumulation of Aβ and the progression of cerebral amyloid angiopathy—and Alzheimer's disease—pathology.[18]

Various aspects of this mechanistic chain—including those with major implications for identifying candidate treatments for cerebral amyloid angiopathy—remain incompletely understood. These aspects include the determinants of the initial vascular Aβ deposits that appear to serve as seeds for further growth of cerebral amyloid angiopathy,[43] the precise steps in vessel remodelling that are responsible for symptomatic intracerebral haemorrhage,[76] and the physiological mechanisms that produce the non-haemorrhagic brain injuries. The mechanisms linking structural and functional changes in small vessels to non-haemorrhagic brain injury might be particularly complex. Candidate mechanisms derived from experimental systems include ischaemia due to lost blood flow at strategic sites within the small vessel network,[84] blood–brain barrier leakage,[85] and increased pulsatility.[86,87] Another intriguing question is the precise determinant of intracerebral haemorrhage, because age of first intracerebral haemorrhage varies substantially even among individuals carrying the same Dutch-type cerebral amyloid angiopathy mutation.[13]

Our framework derives from studies of hereditary and sporadic cerebral amyloid angiopathy; however, many of the pathological and physiological processes are shared with arteriolosclerosis, the other common age-related cerebral small vessel disease.[88] Like cerebral amyloid angiopathy, cerebral arteriolosclerosis is associated with pathological replacement of cells of the tunica media by hyaline material,[77] impaired vascular reactivity to physiological stimulation,[89,90] and both non-haemorrhagic and haemorrhagic brain injury.[77] The lipohyalinosis (ie, fibrinoid necrosis) pathological changes linked to arteriolosclerosis-related haemorrhage involve infiltration of fibrin into the vessel wall, notably reminiscent of cerebral amyloid angiopathy-related vascular remodelling.[60,76] This similarity suggests potential shared mechanisms. Future studies of the progression of arteriolosclerosis will establish how each disease stage responds to candidate interventions. Intriguing preliminary evidence shows that intensive blood pressure lowering could modify small vessel dysfunction even late in the disease course.[91,92]

Contributors

EAK, MJHW, and SMG contributed to conceptualisation and writing of the original draft. JPC contributed to formal analysis and writing of the original draft. SJvV contributed to writing the original draft. DJW contributed to writing the original draft. All other authors contributed to writing, reviewing, and editing the manuscript.

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