BRAIN
REVIEW ARTICLE

Clinical considerations in early-onset cerebral amyloid angiopathy

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Cerebral amyloid angiopathy (CAA) is an important cerebral small vessel disease associated with brain haemorrhage and cognitive change. The commonest form, sporadic amyloid-β CAA, usually affects people in mid- to later life. However, early-onset forms, though uncommon, are increasingly recognized and may result from genetic or iatrogenic causes that warrant specific and focused investigation and management.

In this review, we firstly describe the causes of early-onset CAA, including monogenic causes of amyloid-β CAA (*APP* missense mutations and copy number variants; mutations of *PSEN1* and *PSEN2*) and non-amyloid-β CAA (associated with *ITM2B*, *CST3*, *GSN*, *PRNP* and *TTR* mutations), and other unusual sporadic and acquired causes including the newly-recognized iatrogenic subtype. We then provide a structured approach for investigating early-onset CAA, and highlight important management considerations.

Improving awareness of these unusual forms of CAA amongst healthcare professionals is essential for facilitating their prompt diagnosis, and an understanding of their underlying pathophysiology may have implications for more common, late-onset, forms of the disease.

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Introduction

Descriptions of amyloid deposition within the cerebral vasculature have existed for more than a century[1]; these amyloids are fibrillary protein assemblies composed of stacks of monomers with a beta-sheet structure. They demonstrate distinct ultra-structural properties and a characteristic cross-β X-ray crystallographic diffraction pattern, as well as specific reactions to certain dyes, including Thioflavin T and Congo red.[2] As of September 2020, the International Society of Amyloidosis has identified 36 amyloid

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proteins that can cause human disease,[2] of which six can involve the cerebral vasculature, either exclusively or as part of a systemic amyloidosis. In recent years, however, cerebral amyloid angiopathy (CAA) has become near synonymous with the cerebrovascular deposition of one of these amyloids, amyloid-β, notable also for its frequent pathological presence in Alzheimer's disease. Sporadic amyloid-β CAA in this context refers to disease where a single explanatory cause has not been identified, and is usually age-related. As by far the commonest form of cerebrovascular amyloidosis,[3] sporadic amyloid-β CAA is primarily associated with brain haemorrhage (Fig. 1A and B) but also cognitive impairment, both of which can occur in association with, or independently of, Alzheimer's disease.[4] Predominantly involving the small cortical and leptomeningeal vessels, amyloid-β CAA can be identified in life by characteristic haemorrhagic structural imaging markers on blood-sensitive MRI sequences, namely cortical superficial siderosis and lobar cerebral microbleeds (Fig. 1C and D). These haemorrhagic imaging markers, together with more obviously symptomatic bleeding events, namely parenchymal intracerebral haemorrhage (ICH) and acute convexity subarachnoid haemorrhage, form the basis of the diagnostic Boston criteria.[7,8] Other non-haemorrhagic imaging features, such as cerebral atrophy, white matter hyperintensities and MRI visible perivascular spaces in the centrum semi-ovale (CSO-PVS), are also commonly observed in sporadic CAA[8-10]; whilst these are not necessarily specific for CAA, white matter hyperintensities in a 'multispot' pattern and CSO-PVS are included in the most recent Boston criteria (Version 2.0).[8] There are also CT-based diagnostic criteria for CAA (the Edinburgh criteria[11]), but these require knowledge of *APOE* genotype in order to be applied fully; validation of using the imaging components alone is ongoing, but there is an early suggestion that they do have some diagnostic accuracy.[12-15]

Pathologically, amyloid-β can be immunohistochemically identified with specific antibodies, and descriptions include details of both which vessels (small arteries, arterioles, capillaries, venules, veins) and which locations (meningeal, cortical/parenchymal) and brain regions are involved.[16] Classifications of pathological severity consider both the extent of amyloid deposition within the vessel, which begins in the abluminal layer of the tunica media and progresses to involve all layers of the vessel wall, and the degree of the associated vasculopathy, which can be characterized by fibrinoid necrosis, microaneurysm formation and concentric splitting of vessel wall ('double barrelling') at its most severe.[17-19] Sporadic amyloid-β CAA has a predominantly posterior distribution, with the occipital lobe most commonly affected.[20]

As MRI is more widely used for the clinical assessment of a range of neurological conditions, an increasing number of people are identified as having imaging features of CAA, which can be an incidental or unexpected finding. Although clinical context is essential for determining their importance, in younger patients presenting with ICH, cognitive symptoms or transient focal neurological episodes, the presence of these markers might indicate certain rare but important causes of CAA that warrant specific and focused investigation with implications for patients and their families. Young or early-onset in this context is often considered to be before the age of 50 years, when sporadic amyloid-β CAA would be unusual or unexpected,[8] although strict age criteria are necessarily arbitrary. The amyloid-β protein has a central and defining role in both CAA and Alzheimer's disease, a role underpinned by the identification of mutations in genes involved in amyloid-β production.[21-23] However, the existence of other, non-amyloid-β forms of CAA also has important mechanistic implications. In this review, our aim is firstly to describe the causes of early-onset CAA (summarized in Fig. 2), including rare monogenic causes and other unusual types of CAA that can affect younger people. Our second aim is to suggest a structured approach to the investigation and management of people who meet the diagnostic clinico-radiological criteria for CAA, and present with early-onset disease.

CAA can be mimicked by other conditions, and in young onset cases it is important to consider other monogenic disorders, including those associated with familial cerebral cavernous malformations (which can resemble cerebral microbleeds on imaging) and those which can cause ICH in the context of other (non-CAA) cerebral small vessel diseases, including *COL4A1/COL4A2* haemorrhagic microangiopathy and CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy).[24,25] Other, non-genetic, diagnoses to consider include reversible cerebral vasoconstriction syndrome (RCVS), cerebral venous thrombosis, vascular malformations (e.g. dural arteriovenous fistulas), posterior reversible encephalopathy syndrome (PRES) and infective endocarditis[26]; these can all result in ICH, acute convexity subarachnoid haemorrhage and cerebral microbleeds. Cerebral microbleeds can also occur following cardiac procedures,[27-29] head trauma[30,31] and critical illness, for example due to severe COVID-19 infection.[32-34] Although none of these conditions typically mimic the strictly lobar microbleed distribution characteristic of CAA, in practice this distinction may not be clear-cut.

Monogenic forms of cerebral amyloid angiopathy

Amyloid-β cerebral amyloid angiopathy

All monogenic forms of CAA are rare, although definitive data on their prevalence are lacking. Mutations relevant to amyloid-β CAA can be considered in two broad categories, on the basis of dominant clinical and pathological phenotype. The first are those where pathological vascular amyloid-β deposition and/or presentation with ICH are the dominant feature(s); these mutations nearly exclusively involve the amyloid-β coding domains of the amyloid precursor protein gene (*APP*). Mutations of *APP* outside of the amyloid-β coding domain that cause familial Alzheimer's disease can show significant pathological evidence of CAA, but the phenotype is cognitive rather than haemorrhagic; this includes the London NM_000484.4(APP):c.2149G>A (p.Val717Ile) mutation,[35] the Indiana NM_000484.4(APP):c.2149G>A (p.Val717Phe) mutation[36] and Swedish NM_000484.4(APP):c.2010_2011inv (p.Lys670_Met671delinsAsnLeu) double mutation.[37,38] The second group are mutations primarily associated with familial Alzheimer's disease, where CAA can be a significant feature. Of these, copy number variants of *APP* (including trisomy 21) are most frequently associated with clinical and radiological haemorrhagic features typical for sporadic CAA; mutations of *PSEN1* and *PSEN2* will also be considered. It is important to recognize that these groups are not necessarily distinct and often overlap; this clinical heterogeneity can result in different presentations (haemorrhagic, cognitive or both) even within a single family carrying a particular mutation.

In monogenic forms of CAA, the genetic mutation or duplication plays a causal role in the disease. Genetic variants that confer increased risk are also likely to make important contributions to early-onset CAA. This has been less studied in CAA compared with Alzheimer's disease,[39,40] but one well recognized risk gene is *APOE*. *APOE* encodes apolipoprotein E (ApoE), a glycoprotein with

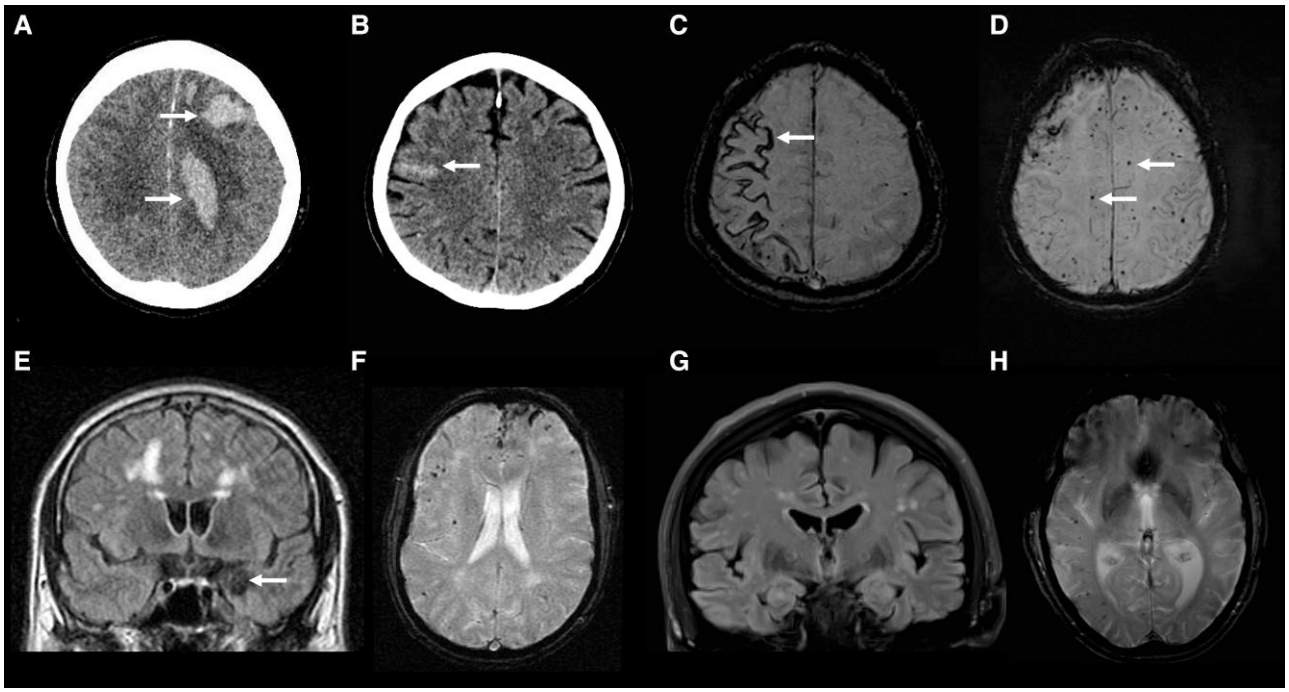

Figure 1 Imaging features of amyloid-β CAA. (**A**–**D**) Examples of brain imaging from individuals with sporadic amyloid-β CAA. CT images demonstrating (**A**) acute ICH and (**B**) acute convexity subarachnoid haemorrhage. Susceptibility-weighted MRI images demonstrating (**C**) disseminated cortical superficial siderosis of the right cerebral hemisphere and (**D**) lobar (cortical) cerebral microbleeds. **B** and **C** reprinted and adapted from Banerjee *et al.*[4] (open access article distributed under the terms of the Creative Commons CC BY 4.0 license). (**E**–**H**) MRI from individuals with features of CAA accompanying familial Alzheimer's disease. An old amygdala haemorrhage (arrow) and extensive white matter hyperintensities on T_2 FLAIR (**E**), with multiple microbleeds on T_2* imaging (**F**) in an *APP* duplication carrier. White matter hyperintensities on T_2 FLAIR (**G**) and widespread lobar microbleeds on susceptibility-weighted imaging (**H**) in an individual with the *PSEN1* R269H mutation. **E** and **F** reprinted and adapted from McNaughton *et al.*[5] **G** and **H** reprinted and adapted from Ryan *et al.*[6] by permission of Oxford University Press.

an important role in peripheral cholesterol metabolism, which also acts as the main lipid and cholesterol transporter within the CNS.[41] The commonest isoform of ApoE is ApoE3; carrying the *APOEε4* genotype (encoding the ApoE4 isoform) is a major risk factor for Alzheimer's disease.[41] In CAA, associations with both *APOEε2* and *APOEε4* genotypes have been described,[39] with evidence most convincing for the latter[42]; both these risk alleles can be associated with earlier age of first ICH in CAA.[43,44] The relevance of other genetic risk factors identified in studies of Alzheimer's disease remains an area for active study; of these, there are initial data suggesting that *ABCA7*, *CLU* and *CR1* might be of relevance to CAA[45-48] and lobar ICH.[49]

Mutations with cerebral amyloid angiopathy as the dominant clinical or pathological phenotype

To date, all identified mutations that primarily result in amyloid-β CAA involve the amyloid precursor protein gene (*APP*); *APP* mutations associated with severe CAA are summarized in Table 1. There are six mutations with confirmed pathogenicity (Fig. 3) and several of uncertain pathogenicity, described in detail below. With the exception of the Dutch-type CAA, only a small number of cases have been reported for each mutation and therefore the full spectrum of presentations might be broader than that currently described.

The amyloid precursor protein can undergo cleavage via two alternative pathways, which are in competition with one another[87]: the first involves cleavage by α-secretase, and does not result in amyloid-β production; the second requires sequential cleavage by BACE1 (β-site amyloid precursor protein cleaving enzyme 1, also known as β-secretase) and gamma-secretase enzymes, which produces amyloid-β peptides. γ-Secretase, which contains either presenilin 1 or 2 as its catalytic subunit, carries out a series of successive cleavages generating shorter amyloid-β peptides. The amyloid-β peptides released can be between 37 and 49 amino acids in length but under physiological conditions the 40 amino acid (amyloid-$\beta_{1–40}$, normally 80% to 90% of the amyloid-β peptides) and 42 amino acid (amyloid-$\beta_{1–42}$, up to 10%) fragments are most common.[87] The coding region for amyloid-β within the *APP* gene can start at either codon 672 or codon 682, depending on BACE1 cleavage, which can occur at either site, and ends variably between codon 709 and 720 depending on γ-secretase cleavage (Fig. 3).[87] Whilst *APP* mutations around the γ-secretase cleavage site typically cause familial Alzheimer's disease presenting with memory impairment, mutations that occur within the amyloid-β coding domain give rise to severe CAA, which can manifest with ICH, dementia or both.

Dutch mutation; NM_000484.4(APP):c.2077G>C (p.Glu693Gln)

Dutch-type CAA (D-CAA; previously called hereditary cerebral haemorrhage with amyloidosis-Dutch type, HCHWA-D) is arguably the archetypal monogenic form of amyloid-β CAA, and remains the most studied clinically.[22] The clinical findings were first described in 1964 in two families originally from the seaside villages of Katwijk and Scheveningen in The Netherlands.[22,88] Although most people with the mutation still live in The Netherlands, there is a kindred now based in Western Australia, who are descendants from a branch of the family who emigrated from Katwijk some

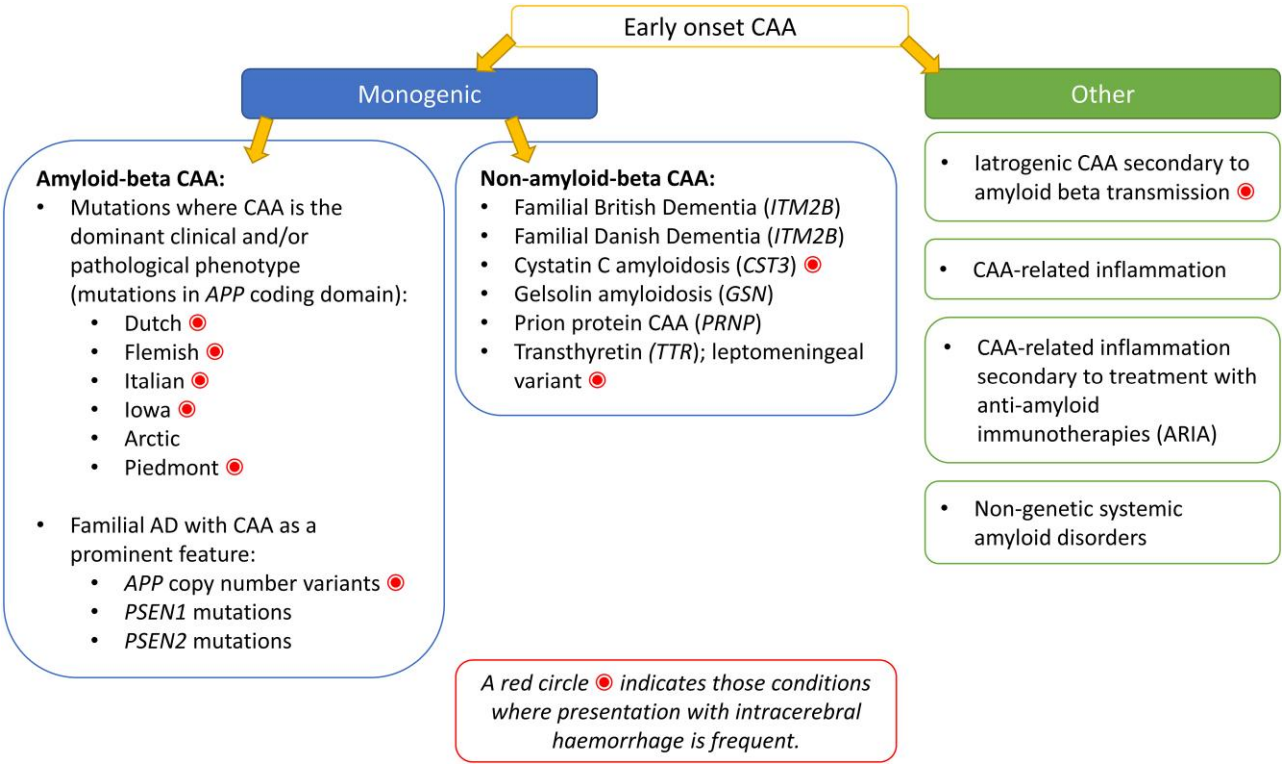

Figure 2 Potential causes of early-onset CAA. AD = Alzheimer's disease; ARIA = amyloid-related imaging abnormalities; CAA = cerebral amyloid angiopathy.

years previously.[89] D-CAA classically presents with recurrent ICH,[90,91] although migraine with aura can also be a presenting feature,[50] as noted in some of the earliest case descriptions.[51] ICH can be followed by seizures (observed in around half of ICH survivors), cognitive decline and dementia, although cases of cognitive impairment in the absence of ICH have also been described.[22,90,92,93] Pathologically, there is severe CAA with a relative paucity of neuritic plaques and neurofibrillary tangles rarely seen, although diffuse amyloid-β deposits may be found.[94,95]

All haemorrhagic and non-haemorrhagic structural imaging markers observed in sporadic age-related amyloid-β CAA have been reported in symptomatic mutation carriers, in addition to a number of novel neuroimaging biomarkers (Table 1). Data from pre-symptomatic mutation carriers has provided important insights into possible biomarkers for early disease, including decreased levels of CSF[62] and plasma[96] amyloid-β_{1-40} and amyloid-β_{1-42}, increased retention of the PET agent Pittsburgh compound B (PiB) on amyloid imaging,[61] reductions in occipital vascular reactivity when presented with visual stimuli,[58] non-haemorrhagic imaging markers (white matter hyperintensities, CSO-PVS and microinfarcts)[52,97] and retinal changes on optical coherence tomography (OCT).[64]

Flemish mutation; NM_000484.4(APP):c.2075C>G (p.Ala692Gly)

This mutation was first described in 1992 in a Dutch family, and of the six patients described, four presented with dementia and two with ICH.[65] Further review of this family[66,98] has confirmed that of the 20 suspected symptomatic mutation carriers, five presented with ICH and a further two family members had strokes (unspecified) during the course of their disease. The mutation was later described in a second unrelated British family,[67] in which six of seven patients presented with dementia and one with ICH. This mutation has also been described in a French man of Portuguese descent.[68] MRI studies have shown extensive white matter hyperintensities, which are present to a lesser extent (but more than expected for age) in pre-symptomatic mutation carriers[66,67,69]; multiple cortical and juxtacortical microbleeds, cortical superficial siderosis and atrophy (cortical and hippocampal) have also been reported.[68] The pathology is characterized by severe CAA and 'dense-core' plaques, which are frequently centred around vessels and predominantly composed of amyloid-β_{1-40}; diffuse amyloid-β deposits and neurofibrillary tangles are also observed.[98,99]

Italian mutation; NM_000484.4(APP):c.2077G>A (p.Glu693Lys)

Twenty symptomatic individuals from four families from Lombardy, Italy, with this mutation have been described, as well as a brother and sister investigated in France,[68] in which affected individuals can present with strokes (haemorrhagic and ischaemic) and progressive cognitive impairment, as well as headaches and seizures (which in some cases appear secondary to the incident haemorrhage).[70] MRI can show white matter hyperintensities and cerebral microbleeds, and cortical occipital calcifications.[68,70] Pathologically there is abundant CAA, and diffuse parenchymal deposition of amyloid-β, but no neuritic plaques or neurofibrillary tangles.[70]

Arctic mutation; NM_000484.4(APP):c.2078A>G (p.Glu693Gly)

This mutation has been reported in a single family, originally from northern Sweden (hence 'Arctic', allowing differentiation from a different *APP* mutation known as the 'Swedish', which is located outside the amyloid-β coding domain adjacent the β-secretase cleavage site).[37] The Arctic mutation causes progressive amnestic

Table 1 Pathogenic missense mutations in the *APP* gene associated with severe CAA

Name	Mutation	Aβ peptide	Pathology			Clinical presentation				Biomarkers	
			CAA	Amyloid plaques	Tau	Typical presentation and AAO, y	ICH, including cSAH	Dementia	Other	Imaging	Other
Confirmed pathogenicity; NM_000484.4(APP)											
Dutch	c.2077G>C (p.Glu693Gln)	E22Q	+	–	–	Recurrent ICH from ~50 (range 39–76) followed or preceded by cognitive impairment.[22]	+	+	Migraine with aura (can manifest 8–9 y prior to first ICH),[50,51] seizures.	cSS, microbleeds, WMH, CSO-PVS, microinfarcts.[52-55] Cortical thinning.[56] DTI abnormalities,[57] changes in rCBF and vascular reactivity.[58] Intragyral haemorrhage, occipital cortical 'stripes' (7 T),[59] correlating with pathological evidence of calcium and iron accumulation within penetrating cortical arteries.[60] PiB-PET positivity.[61]	Reduced CSF $A\beta_{1-40}$ and $A\beta_{1-42}$.[61,62] Reduced plasma $A\beta_{1-42}$.[63] Retinal changes on OCT.[64]
Flemish	c.2075C>G (p.Ala692Gly)	A21G	+	+	+	ICH, dementia or both. Mid-40s (range 35–61)[22,65-68]	+	+	Seizures	Extensive WMH on MRI; WMH in pre-symptomatic mutation carriers.[66,67,69] cSS, microbleeds, cortical and hippocampal atrophy.[68] Parieto-temporal hypometabolism on FDG-PET.[68]	Intermediate CSF $A\beta_{1-42}$; normal CSF total-tau and phospho-tau.[68]
Italian	c.2077G>A (p.Glu693Lys)	E22K	+	–	–	Recurrent ICH mid-50s (range 44–63)[68,70]	+	+	Headache, seizures	WMH, cSS, microbleeds, occipital calcifications.[68]	Reduced CSF $A\beta_{1-42}$, increased total and phospho-tau.[68]
Arctic	c.2078A>G (p.Glu693Gly)	E22G	+	+	+	Memory-led cognitive impairment, 50s (range 52–62)[71-73]	–	+	Headache, fatigue, psychiatric symptoms, myoclonus, rigidity.	MRI findings variable.[73-75] WMH in some cases; usually mild-to-moderate, extensive in one case. Haemorrhagic imaging markers have not been reported to date. Cortical atrophy (left precuneus, superior temporal and fusiform gyri).[40] PiB-PET normal; reduced glucose metabolism (FDG-PET).[74]	Reductions in CSF $A\beta_{1-42}$, elevations in CSF total tau and phospho-tau.[74,76] Reduced plasma $A\beta_{1-40}$ and 1 $A\beta_{1-42}$, also in pre-symptomatic carriers.[72]
Iowa	c.2080G>A (p.Asp694Asn)	D23N	+	+	+	ICH, dementia or both. Early 50s (range 38–67).[68,77-82]	+	+	Seizures, expressive language dysfunction, personality change, myoclonus, gait abnormalities.	WMH, microbleeds, cortical calcifications.[77-81,83]	
Piedmont	c.2113C>G (p.Leu705Val)	L34V	+	–	–	Recurrent ICH (range 45–72).[84,85]	+	–	TFNE	Diffuse WMH.[84] Lobar microbleeds and cSS on *ex vivo* MRI.[85]	

Aβ = amyloid-β; AAO = age at onset; CAA = cerebral amyloid angiopathy; cSAH = convexity subarachnoid haemorrhage; CSO-PVS = MRI visible perivascular spaces in the centrum semi-ovale; cSS = cortical superficial siderosis; DTI = diffusion tensor imaging; ICH = intracerebral haemorrhage; OCT = optical coherence tomography; PiB = Pittsburgh Compound B; rCBF = regional cerebral blood flow; TFNE = transient focal neurological episodes ('amyloid spells'); WMH = white matter hyperintensities; y = years.

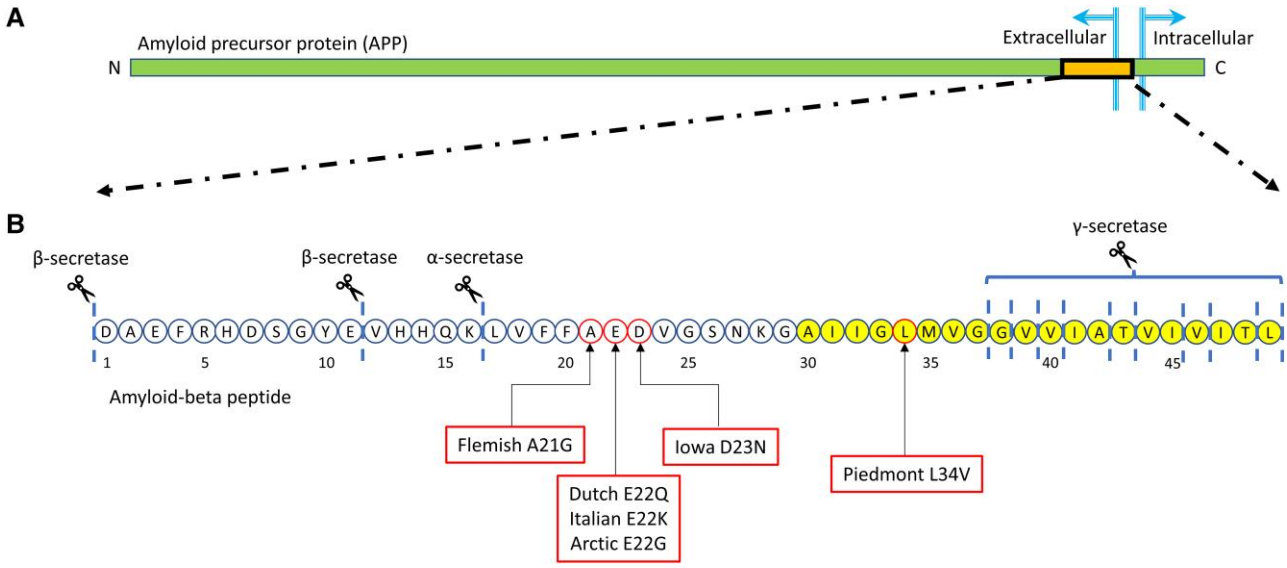

Figure 3 Schematics of the amyloid precursor protein (APP) and amyloid-β peptide. (**A**) Schematic of the amyloid precursor protein (APP). APP is a transmembrane glycoprotein that can exist in multiple isoforms of differing lengths, the most common in the brain being 695 amino acids in length (APP695).[86] This schematic of APP demonstrates its larger extracellular N-terminal end and smaller intracellular C-terminal end (both green). The amyloid-β peptide (orange) starts in the extracellular domain and enters the transmembrane domain. (**B**) Schematic of the amyloid-β peptide and its amino acid sequence. The α-secretase cleavage site, in addition to those for β-secretase (two potential sites) and γ-secretase (multiple sites, resulting in amyloid-β fragments between 37 and 49 amino acids in length) are shown. Amino acids coloured yellow fall within the transmembrane section of APP. Mutations affecting the amino acids outlined in red have confirmed pathogenicity and are particularly associated with CAA.

cognitive impairment.[71,72] Pathologically, there is severe CAA, together with distinctive amyloid-β plaques (lacking a dense core and described as 'ring-like' or 'targetoid') and neurofibrillary tangles.[73,100,101] Intriguingly, very low PiB retention was observed on amyloid PET imaging of two Arctic mutation carriers, despite clearly pathological levels of CSF amyloid-β, total tau and phospho-tau[74]; given that PiB binds fibrillary amyloid,[102] this highlights the potential importance of non-fibrillar forms of amyloid-β in the disease process associated with this particular mutation.[74]

Iowa mutation; NM_000484.4(APP):c.2080G>A (p.Asp694Asn)

First described in a family from Iowa of German descent,[77] this mutation has subsequently been described in a French family of Spanish descent,[78,83] and later in families of Austro-Hungarian,[68] Irish,[79] Polish[80] and Spanish (Basque)[81] descent. The clinical presentation can be either with ICH (as observed in the Austro-Hungarian, French-Spanish, Irish, Polish and Spanish-Basque kindreds), non-aneurysmal subarachnoid haemorrhage (Austro-Hungarian) or dementia (Austro-Hungarian, Iowa and Irish kindreds); other features include seizures, a short-stepped gait, expressive language dysfunction, personality change, and extracerebral vascular changes (external carotid artery dysplasia, thickening of basement membranes in skin capillaries). MRI can show white matter changes (which can be severe), cerebral microbleeds, and posterior 'tram-line' or gyriform cortical calcifications.[77-81,83] Pathologically, there is evidence of severe CAA, together with diffuse plaques and neurofibrillary tangles of varying severity.[77,79,81]

Piedmont mutation; NM_000484.4(APP):c.2113C>G (p.Leu705Val)

This was first described in an Italian family with affected members presenting with recurrent ICH.[84] A subsequent, and apparently unrelated, family has since been described, although confirmatory genetic testing has only been completed in a single case.[85] The clinical presentation is with ICH (cognitive impairment is described in one case, but in the context of multiple ICH). Diffuse white matter hyperintensities have been reported[84]; lobar microbleeds and cortical superficial siderosis have also been described on *ex vivo* MRI.[85] The pathological findings demonstrate CAA without parenchymal plaques or tau pathology.[84,85]

Mutations of uncertain pathogenicity

The 'Greek' mutation, NM_000484.4(APP):c.2062T>G (p.Leu688Val), has been reported in two Greek families, in which individuals had been diagnosed clinically with Alzheimer's disease and vascular dementia.[103,104] The presentation is with mood and gait disturbances, dementia and ischaemic strokes. Although the MRI findings were similar to those observed in another monogenic cerebral small vessel disease, CADASIL, with extensive white matter hyperintensities with involvement of the anterior temporal lobes, no relevant mutations in the causative *NOTCH3* gene were found.[103] Cerebral microbleeds and occipital calcifications were also observed on MRI.[103,104] The *APP* mutation identified is considered to be pathogenic and the CSF findings are also supportive of amyloid-β disease. The neuropathological findings associated with this mutation have not yet been reported, and will provide important confirmatory evidence for establishing whether this mutation is causative in these cases.

The NM_000484.4(APP):c.2137G>A (p.Ala713Thr) mutation has also been described in the context of Alzheimer's disease,[105-108] but remains of uncertain significance as its frequency in the population suggests limited penetrance.[109] A single case with pathological evidence of severe CAA has been described[108]; this patient had a peri-procedural brain haemorrhage at the time of brain biopsy.

Three mutations in the 3′ untranslated region (UTR) of the *APP* gene have been described,[110] one of which is potentially of pathogenic relevance (c.*331_*332del); this patient had early onset CAA characterized by recurrent ICH, with presentation at 39 years.

However, this patient also had a history of childhood neurosurgery for spina bifida, and therefore iatrogenic CAA might be an alternative explanation for their presentation; the latency between surgery and clinical presentation would be in keeping with this latter hypothesis.[111]

Mutations resulting in familial Alzheimer's disease, in which cerebral amyloid angiopathy can be a prominent feature

APP copy number variants, including duplications and triplications

APP duplications are associated with early onset Alzheimer's disease and prominent CAA,[5,112-118] with ICH described in approximately one-third of cases.[119] Seizures are also commonly observed.[120] White matter hyperintensities and cerebral microbleeds have been reported in some of these patients.[5,53,114,121] In trisomy 21 (Down syndrome), where people carry three copies of the *APP* gene (given its location on chromosome 21), there is an increased risk of Alzheimer's disease, which also occurs at younger ages.[122] People with trisomy 21 show an increased prevalence of ICH compared with the general population, but not at the levels observed in *APP* duplications.[119,123] Pathologically (Fig. 4), moderate-to-severe CAA is frequently, but not always, observed,[119,124] and MRI features of CAA (white matter changes, cerebral microbleeds, MRI-visible perivascular spaces) have also been reported[122,125] (Fig.1E and F). More recently, two related cases of *APP* triplication have been described,[126] both of whom presented with early onset dementia; in one of these cases, seizures and recurrent ICH developed during the disease course. As with *APP* duplications, white matter hyperintensities and cerebral microbleeds were observed; in one case CSF findings were supportive of cerebral amyloid-β deposition (low CSF amyloid-β_{1-42}, elevated total-tau and phospho-tau), and brain biopsy of the other confirmed significant cerebral vascular amyloid-β deposition.

PSEN1 mutations

Presenilin-1, encoded by the *PSEN1* gene, is an important component of the γ-secretase enzymatic complex (providing its catalytic site)[127]; mutations in this gene remain the commonest cause of autosomal dominantly inherited familial Alzheimer's disease, with over 300 mutations identified to date.[128] Clinical presentation is variable, and can include features such as seizures, myoclonus, spastic paraparesis, extrapyramidal and cerebellar signs.[23,129,130] Whilst individuals typically present with memory symptoms, non-amnestic cognitive presentations may also occur, for example behavioural or dysexecutive syndromes, or language impairment.[131,132] Age at onset is typically in the mid-40s, but can range from the third to eighth decade of life.[133] The presence of severe CAA on neuropathological examination has been described[23,134,135] in a number of *PSEN1* mutations and is particularly, although not exclusively, associated with mutations beyond codon 200; an example of the neuropathological findings is shown in Fig. 4. However, despite these pathological findings, the occurrence of ICH is unusual, and has only been described in two families, who carry the NM_000021.4(PSEN1):c.49976C>T (p.Pro264Leu) and NM_000021.4(PSEN1):c.857T>C (p.Leu286Pro) mutations.[136,137] White matter hyperintensities on MRI are well recognized,[138] particularly in association with mutations beyond codon 200,[69] and cerebral microbleeds have been reported in some cases[6,53,139,140] (Fig. 1G and H). As in sporadic disease, cortical and hippocampal atrophy are characteristic radiological features of familial Alzheimer's disease, although brain volumes may sometimes appear normal to visual inspection in the early stages of the disease.[141] Rates of atrophy, however, are pathologically increased several years prior to symptom onset, so serial MRI may be helpful in cases of diagnostic uncertainty.[142]

PSEN2 mutations

The *PSEN2* gene encodes the presenilin-2 protein, a homologue of presenilin-1 that can also form the catalytic part of the γ-secretase enzymatic complex.[127] Mutations in this gene most commonly result in familial Alzheimer's disease with a phenotype that is typically amnestic but can include psychosis and seizures. Severe CAA with ICH has been reported in two people carrying the NM_000447.3(PSEN2):c.422A>T (p.Asn141Ile) mutation[143,144]; this mutation, first identified in families of Volga German descent, accounts for the majority of reported *PSEN2* cases.[145] *PSEN2* mutations are much rarer than mutations in *PSEN1* and *APP*, and typically present at a later age, on average in the mid-50s, but which can vary widely within families and be as late as the early 80 s.[133,145] Mutations in this gene should therefore be considered in individuals with early-onset CAA with a family history of late onset Alzheimer's disease.

Non-amyloid-β cerebral amyloid angiopathy

As noted in the 'Introduction' section, although CAA more recently has become near synonymous with amyloid-β CAA, its definition describes any condition in which proteins with biochemical features of amyloid are deposited within the cerebral vasculature. Of the six amyloid proteins that can involve the CNS, four cause localized disease and two can cause CNS disease as part of systemic amyloidosis[2]; these are summarized in Table 2. As with monogenic forms of amyloid-β CAA, obtaining recent and accurate figures for prevalence is challenging, but these are generally accepted to be very rare conditions. The number of reported cases is small and investigation in some cases is limited, and so current descriptions might not reflect the true extent of the clinical phenotype.

ITM2B: familial British and familial Danish dementias

Different mutations in the integral membrane protein 2B (*ITM2B*; previously called *BRI2*) gene result in ABri and ADan amyloidoses, associated with Familial British and Familial Danish Dementia (FBD and FDD), respectively. In both cases, the mutations result in an elongated version of the precursor protein (BRI2), and subsequent cleavage by furin and furin-like endoproteases results in the production of the pathogenic amyloid fibril (ABri and ADan).[146-148]

FBD was first described by Worster-Drought in 1933, and is characterized by a progressive dementia, spasticity and cerebellar ataxia.[149] It is caused by a mutation at codon 267, NM_021999.5 (ITM2B): c.799T>A (p.Ter267Arg), which extends the BRI2 protein to 277 amino acids.[150] Extracranial systemic vascular ABri deposition also occurs, and can involve the pancreas, adrenal glands, lungs, myocardium, liver, spleen and skeletal muscle.[151] 'Stroke-like episodes' are a recognized feature (approximately a quarter of historical cases)[152,153] but their aetiology remains unclear, and in particular, whether they resemble the transient focal neurological episodes (TFNE) or 'amyloid spells' observed in sporadic amyloid-β CAA; this has been hypothesized to be the case in at least one patient.[154] ICH has been reported in two patients,[152,154] one of which primarily involved the anterior putamen and globus pallidus (i.e. non-cortical areas).[152] Two further cases of intracranial bleeding were due to subdural haemorrhage and intracranial saccular

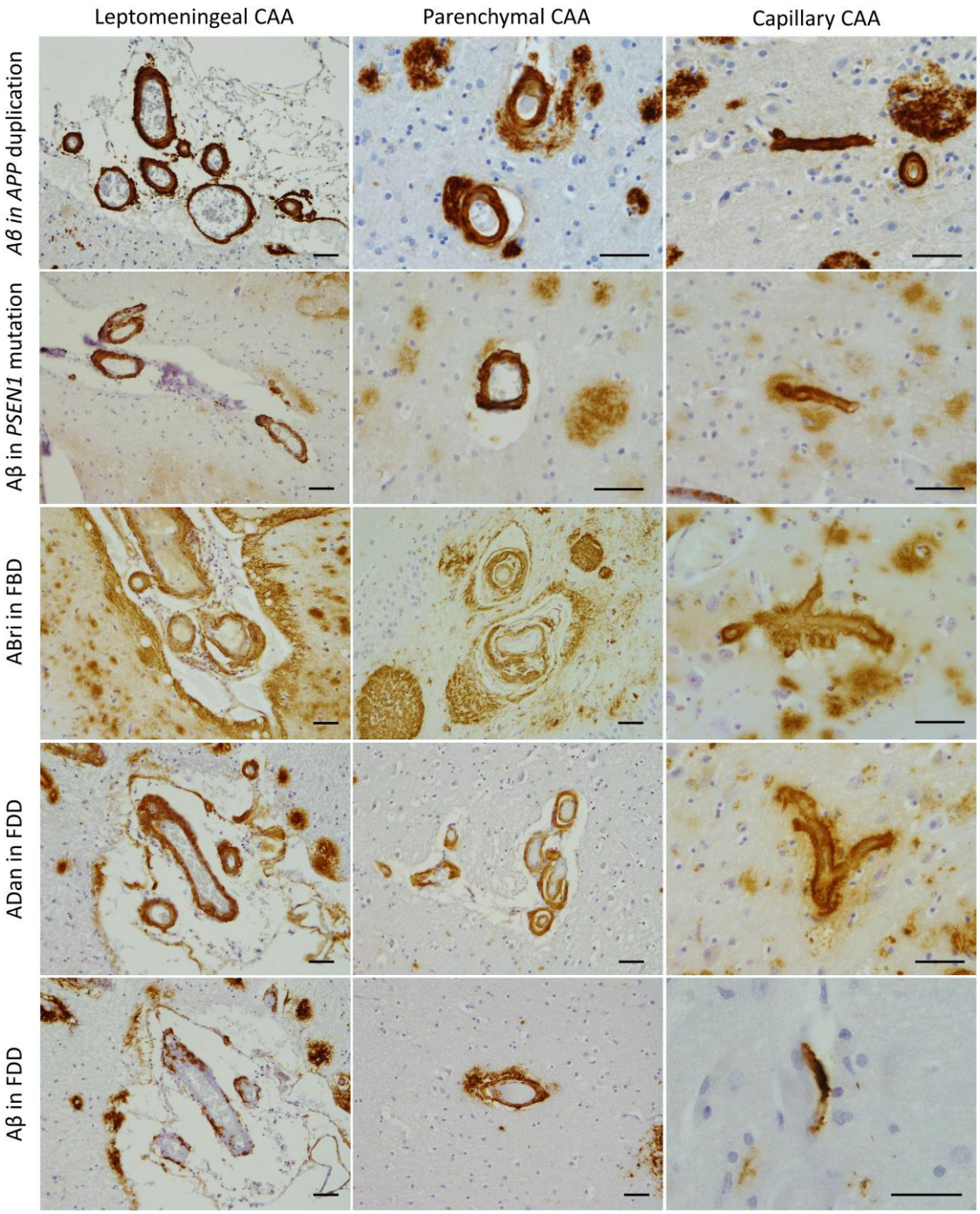

Figure 4 Immunohistochemical staining of early-onset cerebral amyloidosis. Amyloid-β (Aβ) immunohistochemistry in an *APP* duplication and *PSEN1* post-codon mutation case showing severe cerebral amyloid angiopathy (CAA) in both leptomeningeal and parenchymal blood vessels; there is also evidence of amyloid-β deposition in the capillaries. In familial British dementia (FBD) the amyloidogenic protein ABri is deposited in leptomeningeal and parenchymal blood vessels, as well as capillaries. In familial Danish dementia (FDD), both ADan and amyloid-β are found deposited as amyloid. ADan and amyloid-β are found within the same blood vessels shown in the leptomeningeal vessels on sequential sections. ADan and amyloid-β are also found in parenchymal vessels and capillaries. Scale bars = 50 µm.

aneurysm rupture, and details for a third potential intracranial haemorrhage are unconfirmed.[152,153] MRI brain findings include white matter hyperintensities, which can be extensive and involve the corpus callosum, the presence of lacunar infarcts and cerebral microbleeds.[152-154] Pathological observations (Fig. 4) include vascular amyloid deposition in the brain, spinal cord and leptomeninges, parenchymal (most frequently involving the hippocampus and cerebellum) and perivascular plaques of varying morphology, and diffuse non-fibrillar parenchymal deposition, as well as neurofibrillary tangles (particularly involving limbic areas) and ischaemic white matter changes.[146,152,153,155]

FDD, originally called heredopathia ophthalmo-oto-encephalica, was first described by Strömgren and colleagues in 1970,[156] and is characterized clinically by cataracts, deafness, progressive ataxia

Table 2 Causes of non-amyloid-β CAA

Name	Gene	Protein		Clinical features		Imaging
		Fibril	Precursor	Those shared with sporadic Aβ CAA	Others	
Familial British Dementia	*ITM2B*	ABri	ABriPP	'Stroke-like episodes' (possibly TFNE), ICH (rare), dementia	Spasticity, cerebellar ataxia	Extensive white matter hyperintensities Lacunar infarcts Cerebral microbleeds
Familial Danish Dementia Heredopathia ophthalmo-oto-encephalica	*ITM2B*	ADan	ADanPP	Dementia	Cataracts, deafness, progressive ataxia, paranoid psychosis (as part of dementia syndrome)	White matter hyperintensities
Cystatin C amyloidosis 'Icelandic type', HCHWA-I, HCCAA	CST3	ACys	Cystatin C	Recurrent ICH, progressive cognitive impairment	None	White matter changes
Gelsolin amyloidosis 'Finnish type', FAF, HGA, Meretoja syndrome	GSN	AGel	Gelsolin	None	Corneal lattice dystrophy, progressive cranial neuropathy, peripheral neuropathy (predominantly sensory), cutis laxa, myokymia, autonomic dysfunction, gait ataxia, cardiac and renal disease	White matter changes Cerebral microbleeds
PrP-CAA	*PRNP*	APrP	PrP	Dementia (Y145X, Q160X, Y163X)	Diarrhoea, autonomic dysfunction, peripheral neuropathy (Q160X, Y163X)	Non-specific white matter changes (Y163X, Y226X)
Leptomeningeal variants of hereditary transthyretin ATTR amyloidosis *De novo* leptomeningeal involvement following liver transplantation in other variants of hereditary TTR amyloidosis	*TTR*	ATTR	Transthyretin	ICH, SAH (can be recurrent), TFNE, progressive cognitive impairment	Headache, ataxia, myelopathy, seizures, psychosis.	Superficial siderosis (supra- and infratentorial) Cerebral microbleeds Meningeal enhancement

Aβ = amyloid-β; CAA = cerebral amyloid angiopathy; CMB = cerebral microbleeds; FAF = familial amyloidosis of Finnish type; HCCAA = hereditary cystatin C amyloid angiopathy; HCHWA-I = hereditary cerebral haemorrhage with amyloidosis-Icelandic type; HGA = hereditary gelsolin amyloidosis; ICH = intracerebral haemorrhage; PP = precursor protein; PrP = prion protein; SAH = subarachnoid haemorrhage; TFNE = transient focal neurological episodes.

and dementia, with paranoid psychosis a common feature.[157] It is caused by a decamer duplication of the nucleotides 786 and 795, NM_021999.5(ITM2B):c.787_796dup (p.Ser266fs), thereby shifting the reading frame and increasing the BRI2 length to 277 amino acids (the same length observed in FBD, although the C-terminal amino acid sequence is different).[157] Whilst ICH has not been reported, there has been a recorded death due to cerebrovascular disease,[156] and ischaemic stroke has also been reported.[158] Brain MRI can show white matter hyperintensities; evidence of cSS or cerebral microbleeds have not been reported. The neuropathological findings (Fig. 4) include widespread amyloid angiopathy of the neocortex, choroid plexus, cerebellum, spinal cord and retina, as well as parenchymal and leptomeningeal deposits and extensive tau pathology.[146,158] The neocortex and retina are more severely affected pathologically in FDD than FBD; another important difference is the presence of parenchymal and vascular amyloid-β in FDD that is not present in FBD. The amyloid-β can be found in association with ADan deposits as well as independently.[158]

More recently, a new mutation in *ITM2B*, NM_021999.5(ITM2B):c.800G>T (p.*267Leuext*11), associated with dementia, ataxia, deafness and paraplegia has been described (familial Chinese dementia).[159] This mutation also results in an abnormal extension of the BRI2 protein. Brain MRI shows white matter hyperintensities but no cerebral microbleeds; confirmation of any neuropathological findings and the nature of the amyloidogenic protein is pending.

Cystatin C amyloidosis

A hereditary disease affecting certain families in Iceland and causing fatal ICH in young people was first described in 1935; the association with cerebrovascular amyloid deposition was made in 1972, with the causative protein and then gene mutation in the *CST3* gene, NM_000099.4(CST3):c.281T>A (p.Leu94Gln), identified in the early and mid-1980s, respectively.[160-162] This condition is now recognized as hereditary cystatin C amyloid angiopathy (HCCAA), also called hereditary cerebral haemorrhage with amyloidosis-Icelandic type (HCHWA-I); cystatin C is an inhibitor of extracellular cysteine proteinases and is found in all body fluids.[163] This presents with ICH in the 20s, with first ICH nearly always before the age of 40,[164] and progressive neurological sequelae as a consequence of multiple strokes[165]; average life expectancy is ~30 years.[166,167] Pathologically there is significant ACys deposition within the small arteries and arterioles of the leptomeninges and brain; deposits are also found within the skin, lymph nodes, spleen, salivary glands and testes.[160,168,169] White matter changes[170] have been reported; it is not clear whether structural haemorrhagic features (cerebral microbleeds, cortical superficial siderosis) are also present.

Gelsolin amyloidosis

AGel or gelsolin amyloidosis, also referred to as familial amyloidosis of Finnish type (FAF), hereditary gelsolin amyloidosis (HGA) and Meretoja syndrome (after Jouko Meretoja, who in 1969 first described the syndrome in three Finnish families[171,172]), occurs due to mutations in the *GSN* gene. *GSN* encodes the gelsolin protein, which binds actin and is involved in cytoskeletal remodelling. Two mutations at the same locus, NM_198252.3(GSN):c.487G>A (p.Asp163Asn) and NM_198252.3(GSN):c.487G>T (p.Asp163Tyr), cause the classical syndrome, although other mutations have more recently been described.[171-175] Onset is typically in the fourth or fifth decade of life, and corneal lattice dystrophy is often the first clinical sign. Stroke, and in particular ICH, is unusual,[172,176,177] as is dementia,[177] although subtle neuropsychological deficits have been reported.[176] Brain MRI features can include white matter changes[178] (although not necessarily in excess of that expected for age[176,179]) and a small number of microhaemorrhages.[176] Classical features include a progressive cranial neuropathy (typically starting with the facial nerve and progressing to involve other lower cranial nerves, thereby compromising speech and swallowing), a mild predominantly sensory peripheral neuropathy, and dermatological involvement, particularly cutis laxa.[172,180] Other features can include myokymia, autonomic dysfunction, gait ataxia and the consequences of cardiac and renal involvement.[172,180] Pathologically, there is deposition of AGel throughout in multiple organs and particularly involving the basement membranes of epithelial, smooth and striated muscle cells[177,181]; in the CNS deposition is predominantly vascular, and involves the grey and white matter of the brain,[182,183] spinal cord and meninges.[182]

Prion protein cerebral amyloid angiopathy

Prion diseases are associated with the propagation of disease-related assemblies of misfolded prion protein (PrP) or prions and can be sporadic, acquired or inherited in aetiology[184]; they have wide phenotypic diversity which can readily mimic other neurodegenerative diseases with the classical syndromes being Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI) and kuru.[184] Whilst the common pathological findings in most cases, regardless of aetiology, are spongiform degeneration, gliosis, neuronal loss and abnormal PrP immunoreactivity (synaptic deposits and/or plaques of multiple morphologies[21,185,186]), amyloid angiopathy can occur. This appears to be an exclusive feature of certain inherited forms of PrP disease, namely stop codon mutations in the *PRNP* gene which result in truncated forms of PrP with loss of the glycosylphosphatidylinositol (GPI) anchor (which allows PrP to attach to the cell membrane), and some octapeptide repeat insertional mutations.[21,169,186-188]

Mutations associated neuropathologically with PrP-CAA include NM_000311.5(PRNP):c.435T>G (p.Tyr145Ter),[187,189-191] NM_000311.5(PRNP):c.478C>T (p.Gln160Ter),[189,191-194] NM_000311.5(PRNP):c.489C>G (p.Tyr163Ter),[195,196] NM_000311.5(PRNP):c.678C>A (p.Tyr226Ter)[197] and NM_000311.5(PRNP):c.534_535del (p.Asp178fs)[188,198,199] The clinical phenotype of these mutations includes dementia, autonomic dysfunction, chronic diarrhoea and peripheral neuropathy and some have been associated with non-specific white matter hyperintensities on MRI (Table 2). To date, other clinical or neuroimaging features associated with sporadic amyloid-β CAA have not been described. Three further stop codon mutations have been described,[196,197,199] but neuropathological data are not available and therefore the presence of PrP-CAA is unknown; imaging data, where reported, have not been typical for CAA.

Transthyretin

Transthyretin (TTR) is a transport protein synthesized by the liver, choroid plexus and retinal pigment epithelium,[200,201] and in humans it can result in amyloidosis in one of two ways. The first is amyloidosis of wild-type TTR, which results in senile systemic amyloidosis (also called wild-type ATTR or ATTRwt amyloidosis) characterized by cardiomyopathy in the elderly (over the age of 80).[201,202] The second is amyloidosis due to variant forms of the TTR protein, caused by mutations in the *TTR* gene and resulting in hereditary ATTR amyloidosis.[201] Hereditary ATTR amyloidosis usually presents with one of three main phenotypes: familial amyloid polyneuropathy (FAP), familial amyloid cardiomyopathy and familial leptomeningeal (sometimes meningovascular, or oculoleptomeningeal/

oculomeningovascular, if there is eye involvement) amyloidosis. This latter presentation is associated with widespread amyloid deposition within the small and medium arteries, arterioles and veins of the leptomeninges, and more variably can involve the brain and eyes.[201,203-208] Leptomeningeal involvement can also occur in people with FAP.[206,209] Several mutations associated with familial leptomeningeal amyloidosis have been identified,[204] and this syndrome can rarely develop *de novo* in other phenotypes after liver transplantation, which is the usual treatment for ATTR amyloidosis (as it removes the main source of variant TTR) due to ongoing TTR synthesis by the choroid plexus and retinal pigment epithelium.[202,210-213] Improved treatment of the systemic amyloid component of ATTR amyloidosis (without effective treatment of CNS TTR synthesis) is leading to increased recognition of the leptomeningeal manifestations, creating an unmet need for treatment.

Clinically, leptomeningeal involvement can present with intracerebral and subarachnoid haemorrhage, which can be recurrent[204,214-218]; progressive cognitive impairment[201,219]; transient focal neurological episodes[210,212] can occur, but not always with radiological evidence of leptomeningeal disease; they may be an early clinical clue to leptomeningeal involvement. Other features can include headache, ataxia, myelopathy, seizures and psychosis.[201,204] Brain MRI can show superficial siderosis (supra- and infratentorial, with the latter resulting in a clinical syndrome analogous to classical superficial siderosis of the CNS) and cerebral microbleeds,[212,215,220,221] in addition to meningeal enhancement with contrast.[204-207,222] White matter hyperintensities do not appear to be a prominent feature.

Other causes of early-onset cerebral amyloid angiopathy

Iatrogenic cerebral amyloid angiopathy

Whilst many proteins associated with neurodegeneration have been shown experimentally to have 'prion-like' properties, there has been no clear evidence for their iatrogenic transmission until recently with the recognition of human transmission of amyloid-β pathology following treatment with human cadaver-derived pituitary growth hormone contaminated with amyloid-β seeds[223] and causing iatrogenic CAA by a prion-like process.[224] This iatrogenic form of CAA has only been recognized relatively recently,[223] and several cases have now been reported.[225,226] Clinical presentation is typically with ICH, occurring after a latency of between two and four decades after exposure to amyloid-β, often in childhood; cases presenting with cognitive impairment and seizures have also been described.[226] Associated medical interventions include neurosurgery, and procedures or treatments involving cadaveric human material, for example dura mater (used either as a surgical material or for embolization of vascular malformations) and pituitary-derived (cadaveric) human growth hormone.[223,225] The MRI and other investigative findings (amyloid-PET, CSF) are similar to those observed in sporadic amyloid-β CAA.[226-238] Pathologically, there is evidence of vascular amyloid-β deposition, but findings can also include parenchymal amyloid-β plaques and tau pathology, which are more commonly observed in Alzheimer's disease.[111]

Inflammatory cerebral amyloid angiopathy

Inflammatory forms of CAA, a spectrum of disease ranging from CAA-related inflammation (CAA-ri) to amyloid-β related angiitis (ABRA), describe forms of CAA where pathologically there is an inflammatory response to vascular amyloid-β.[239,240] Although the vast majority of cases present at an older age (over 65 years[239]; mean age 72.9 years in a recent prospective cohort of 113 patients[241]), younger onset cases have been described, including cases in people with symptomatic and pre-symptomatic familial Alzheimer's disease.[242,243] The current clinico-radiological diagnostic criteria allow the diagnosis to be made from the age of 40 onwards, though the spectrum of disease is widening.[239,244,245]

CAA-related inflammation is thought to occur as a result of the spontaneous generation of auto-antibodies against amyloid-β, supported by the identification by one group of such antibodies in the CSF of some patients with inflammatory CAA,[246-248] and the observation that similar imaging appearances sometimes occur following the administration of anti- amyloid-β antibodies as a treatment for Alzheimer's disease (amyloid-related imaging abnormalities, ARIA).[249] Clinically, CAA-related inflammation classically presents with seizures, altered consciousness, cognitive decline (often rapidly progressive) and focal neurological deficits due to stroke, which are frequently but not exclusively haemorrhagic.[239] Milder forms in which there is a mismatch between the severity of clinical and imaging features have also been reported.[250] This form of CAA can also manifest in people with established cognitive impairment.[251]

The imaging criteria[245] for CAA-related inflammation require the presence of one or more cortico-subcortical haemorrhagic lesions (ICH, acute convexity subarachnoid haemorrhage, cortical superficial siderosis, cerebral microbleeds) and characteristic white matter lesions that extend to the immediately subcortical white matter; these can be unifocal or multifocal, cortico-subcortical or deep, and are usually asymmetric. Some cases seem to respond well to immunosuppression, but there are also cases of spontaneous improvement and treatment failure (either failure to respond, or relapse following an initial response), highlighting the paucity of natural history data for this condition.[239,241,252] The *APOE* ε4 genotype appears to be a risk factor for both inflammatory CAA and ARIA.[239,253-257]

Non-genetic systemic amyloid disorders

There are pathological descriptions of cerebrovascular involvement in patients with light chain (AL) and serum amyloid A (AA) systemic amyloidoses.[258] ICH in the context of AL amyloidosis has been reported,[259] but appears to be a rare complication of this condition.

Aluminium toxicity

Two pathological cases of CAA occurring in the context of aluminium toxicity have been reported, one of which presented clinically at the age of 49 years,[260] following a water pollution incident in 1988 in North Cornwall, UK.[260-262] In this accident, high concentrations of aluminium sulphate were discharged into the drinking water supply over a period of weeks.[261] However, genetic testing in these cases was limited (reflecting the availability of testing at the time) and there have been no further reports of cases following this exposure; given the small number of cases, it is difficult to draw firm conclusions regarding causality. Further details regarding the clinical presentation (particularly details of past medical history) would help to exclude other potentially relevant exposures (particularly iatrogenic ones).

Making the diagnosis and what to do next

Approach to investigation

Whilst there is no consensus on how patients with early-onset CAA should be investigated (perhaps unsurprisingly, given the relative rarity of cases), we recommend the approach outlined in Fig. 5. Some of the recommended tests might only be available in centres with a specialist interest in CAA, and therefore onward referral should be considered.

Early-onset cases can present via acute stroke services (after ICH, transient focal neurological episodes or symptoms of CAA-related inflammation), to memory clinics and other cognitive services, or following identification of imaging features of CAA whilst undergoing investigation for other neurological symptoms (e.g. headache). For those presenting with ICH, causes which are particularly associated with haemorrhagic manifestations of CAA should be initially considered (Fig. 2). Familial Alzheimer's disease associated with CAA might present to cognitive services without clinical or imaging features of haemorrhage[8]; in such cases hippocampal atrophy and white matter changes (Fig. 1E and G) might be important, as is a family history of dementia or stroke (early or late onset). Such patients should all have MRI with blood-sensitive sequences to review for clinically silent markers of CAA (particularly cerebral microbleeds; Fig. 1D, F and H), in addition to standard volumetric and FLAIR sequences.

In all cases, details of other potentially relevant neurological (including migraine and the nature of any aura, transient neurological disturbances) and non-neurological symptoms should be recorded; CAA-related TFNE are stereotyped episodes of cortical disturbance, usually lasting for less than 30 min and classically with a 'spreading' onset and progression.[263] In addition, it is important to establish whether there is history of potential iatrogenic amyloid-β exposure, particularly treatment or operations involving cadaveric pituitary hormones or dura mater and any other previous medical or surgical procedures involving the brain, spinal cord or posterior eye. This may require a diligent search of all available previous medical records, including operation notes from decades earlier. In addition to obtaining a detailed family history of neurological disease, we would advise confirming the patient's ethnic background and family origins.

In cases where there is clinical and radiological evidence of early-onset CAA, with or without a supporting family history, we would recommend genetic testing, either via a neurodegenerative panel, whole exome or whole genome sequencing (WES and WGS, respectively); copy number variants may need to be requested separately, depending on the method used. In centres where only individual gene testing is available, the presence or absence of cognitive impairment in addition to haemorrhagic markers of CAA can be useful in establishing which genes to prioritize. In people with haemorrhagic markers of CAA but no cognitive symptoms, and no family history of dementia, focused initial testing of *APP* (to include both missense and copy number variants) is likely to have the highest yield. In people with cognitive symptoms as well as haemorrhagic CAA, or cases where there is a family history, testing of *APP* (missense mutations and copy number variants), *PSEN1* and *PSEN2* is needed. In individuals with a later age at symptom onset but strong family history, genetic testing may also be considered.

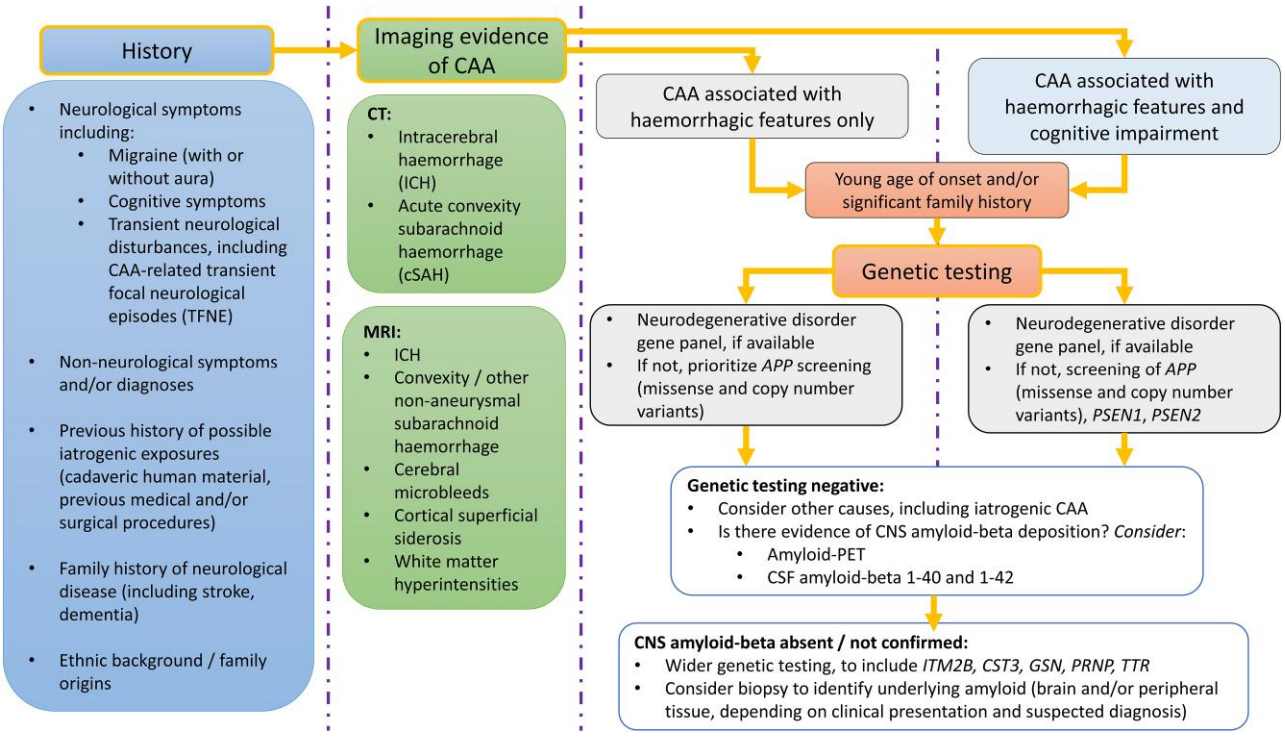

Figure 5 An outline approach to investigating early-onset CAA. The order of investigations will necessarily depend on the clinical context for an individual patient and the investigations available at a particular centre. In cases where gene panel testing is requested, it is important to ensure that the method allows duplications (and other copy number variants) to be identified, as this is not universally the case. CAA = cerebral amyloid angiopathy.

Should this genetic testing be negative, other diagnoses (such as iatrogenic CAA) should be explored. Further investigations to evaluate the presence (or absence) of amyloid-β can be considered, as this potentially allows exclusion of the rarer non-amyloid-β forms of CAA. This can be achieved by CSF measurement of amyloid-β markers, although validated thresholds for the clinical diagnosis of CAA have not been defined. The presence of CSF amyloid-$\beta_{1–42}$ levels, or a CSF amyloid-$\beta_{1–42/1–40}$ ratio consistent with Alzheimer's disease would support cerebral beta-amyloidosis[264,265]; plasma measurement of these markers might also be possible clinically in the future.[266] Amyloid-PET imaging can also be helpful, although this imaging modality might not be available outside non-specialist centres and it is important to recognize that tracers can bind other amyloids and are therefore not specific for amyloid-β.[154,267,268] As with CSF measures, thresholds for CAA diagnosis have not been established,[269] but amyloid-PET imaging consistent with Alzheimer's disease may support the presence of cerebral amyloid-β deposition.[265] In cases where amyloid-β deposition has not been confirmed, broader genetic testing to include other causes of cerebrovascular amyloidosis should be considered.

Rarely, and particularly when other treatable conditions are in the differential diagnosis (e.g. cerebral vasculitis or intravascular lymphoma), it may be appropriate to consider a brain biopsy, with CJD precautions where appropriate. Brain biopsy and other relevant ancillary tests (such as digital subtraction angiography) might be considered in cases with an unusual clinical presentation (for example, rapidly progressive symptoms, or those where encephalopathy or seizures without ICH are a dominant feature), atypical imaging findings (for example, prominent cortical swelling, acute ischaemic lesions, isolated white matter lesions with an inflammatory appearance) and inflammatory changes in the CSF. A previous series of cerebral biopsies undertaken to investigate patients with dementia found that a raised CSF white cell count was the best predictor for identifying a potential treatable, inflammatory process.[270,271]

The nature and provision of genetic testing is changing, and the increasing availability of next generation sequencing techniques including WES and WGS has the potential to change the diagnostic approach in early onset-CAA.[272] In particular 'neurodegenerative disorder' gene panels, which contain *APP*, *PSEN1* and *PSEN2* as well as other genes of interest, can be a more practical option in those with a strong family history, and can be more readily accessible than investigations such as amyloid-PET or CSF amyloid-β measures. Access and approaches to genetic testing may vary between countries. In the UK, the National Health Service (NHS) Genomic Medicine Service aims to provide consistent and equitable access to genomic medicine and has developed the publicly available, annually updated, National Genomic Test Directory (https://www.england.nhs.uk/genomics/the-national-genomic-test-directory/), which lists the available tests, their indications, who can access them and the testing methodologies by which they should be delivered. WGS is being introduced for neurodegenerative disorder panel testing, which brings increased diagnostic capabilities including the ability to detect copy number variants, in contrast to WES. Prior to the introduction of WGS, testing for APP duplications had to be requested and performed separately.[272] For both whole exome and whole genome approaches, careful pre-test discussions regarding variants of uncertain significance and secondary findings (mutations unrelated to the condition being investigated, which could have implications for future health) should be included as part of the informed consent process.[272]

Management considerations

Anti-platelet and anticoagulant medications

Given that CAA is clinically associated with intracranial bleeding, there is understandable anxiety when people with CAA require treatment with medications that increase that bleeding risk, namely anti-platelet and anticoagulant medications. An MRI can be helpful in this context for confirming the diagnosis of CAA, particularly in people presenting with a single lobar ICH. Whilst younger patients (particularly those without systemic amyloidosis) are less likely to have age-associated comorbid conditions that might require the use of such medications (e.g. atrial fibrillation, ischaemic heart disease, peripheral vascular disease), the risk of recurrent haemorrhage in individuals with familial CAA presenting with or without ICH might be significant, although definitive natural history data are lacking.

In the absence of good quality trial data in these specific young-onset cohorts, we base our approach on that used for patients with sporadic CAA. In people who have had one or more ICH, evidence from the RESTART trial[273] suggests no difference in outcomes between those that do and do not restart anti-platelet therapy for the secondary prevention of occlusive vascular disease, even in those with lobar ICH (which has a higher recurrence rate and is associated with CAA). However, this trial included few individuals with CAA. In view of this, our practice is to reserve anti-platelet therapy only for those with strong indications for use, such as significant ischaemic heart disease or previous ischaemic stroke. There are fewer data regarding anticoagulant medications after ICH, and no randomized data specific to CAA; this creates a management challenge for those with long-term or lifelong indications for use (atrial fibrillation, recurrent venous thromboembolism). The APACHE-AF trial of apixaban in survivors of an anticoagulant associated ICH with co-existent atrial fibrillation found that the risk of non-fatal stroke or vascular death was similar regardless of whether a participant received apixaban or not.[274] However, the event rate was low, precluding analysis by original haemorrhage location or presence of CAA. SoSTART,[275] a randomized open-label non-inferiority trial investigating starting versus stopping oral anticoagulation in survivors of intracranial haemorrhage with atrial fibrillation and which included twice as many participants as APACHE-AF, was also inconclusive. In both SoSTART and APACHE-AF, the majority of recurrent ICH events occurred in people randomized to an anticoagulant group. A recent Cochrane synthesis review,[276] which included the APACHE-AF, ReSTART and SoSTART studies (and others) similarly concluded that there is limited evidence to support either benefit or harm when treating with anti-platelets or anticoagulants after ICH. For these reasons, in people with CAA and a long-term or lifelong indication for anticoagulation, a direct oral anticoagulant (DOAC) is preferred over vitamin K antagonists like warfarin due to the ~50% lower risk of intracranial haemorrhage. Alternative approaches that limit the duration of anticoagulation (e.g. left atrial appendage closure) can also be considered, although as yet there are no data for these approaches in early-onset CAA. In people with haemorrhagic MRI markers of CAA (cortical superficial siderosis and cerebral microbleeds; Fig. 1C and D) but no history of symptomatic haemorrhage, we would recommend a similar approach, but one that considers other symptoms. Transient focal neurological episodes and cortical superficial siderosis are both likely to result from episodes of acute convexity subarachnoid haemorrhage (Fig. 1B), which is associated with a high risk of later ICH[277,278]; in view of this, we consider these

patients in the same way as those with a history of symptomatic ICH. For those with cerebral microbleeds only, our approach is more nuanced; the Microbleeds International Collaborative Network (MICON) ischaemic stroke and ICH scores (MICON-IS and MICON-ICH, respectively)[279] provide one approach for evaluating the impact of microbleed presence on ischaemic stroke and ICH risk, but the scores have not been validated outside patients with ischaemic stroke or transient ischaemic attack (TIA).

Vascular risk factors including blood pressure

As with anti-platelet and anticoagulant medications, specific trial evidence for early-onset CAA is lacking, and therefore our practice is based on our approach for people with sporadic CAA. Good blood pressure control in people with prior ICH reduces subsequent haemorrhage risk,[280] including those with ICH due to sporadic CAA,[281] as demonstrated in the PROGRESS trial. There are also observational data that support stricter blood pressure targets in people with ICH (including lobar ICH) to reduce future haemorrhage recurrrence.[282] Although evidence for a specific target blood pressure for secondary prevention in CAA is limited (due to methodological differences in the relevant trials),[283] we aim for a blood pressure target of 130/80 mmHg or lower (as tolerated) in people with sporadic CAA, with or without a prior history of ICH; this target is recommended for all people with ICH in recently published guidelines from the American Heart Association (AHA) and American Stroke Association (ASA).[284] In early-onset CAA, we regularly monitor blood pressure and aim for a similar blood pressure target, particularly in those with prior ICH.

Statin use in people with CAA remains controversial. Two large, randomized placebo-controlled trials (SPARCL,[285] HPS[286]) both suggested an increased risk of ICH with statin use, and there have been subsequent recommendations that statin use should be avoided in those with lobar ICH.[287] Meta-analysis of these and other statin trials did not find an increased risk of ICH, but did note a positive impact of statin use on mortality and functional outcome, although this work did not consider CAA specifically.[288] The recent AHA/ASA guidelines[284] recommend that statin use following ICH should be considered on an individual basis.

The impact of other vascular risk factors for early-onset CAA, as for other types of CAA, is less clear. There is a suggestion that life expectancy of people with cystatin C amyloidosis dramatically reduced during the 19th century, which was thought to reflect environmental changes and specifically an increased consumption of dietary salt and imported foods high in carbohydrates.[167] Whilst this might simply relate to higher rates of hypertension, it does raise a question of whether aggressive management of other cardiovascular risk factors in people with genetic forms of CAA might have prognostic benefits. Our approach is to screen for cardiovascular risk (diabetes, smoking, lipid profile) and treat only where abnormalities are identified. We also advise regular exercise, a healthy diet low in saturated fats, avoidance of alcohol and smoking cessation.

Symptomatic treatments for Alzheimer's disease

Pharmacological treatments such as acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) and the NMDA receptor antagonist memantine[289] are widely licensed for symptomatic management in Alzheimer's disease and should be offered to individuals with familial Alzheimer's disease. Whilst these medications are not routinely offered to individuals diagnosed with CAA and/or vascular dementia alone (trials to date of these agents in vascular dementia show modest cognitive benefits, but with effect sizes felt unlikely to be clinically important and no real change for functional outcomes[290,291]), there are case reports suggesting that acetylcholinesterase inhibitors might provide some benefit in those thought to have Alzheimer's disease co-pathology contributing to cognitive impairment in addition to CAA.[292] Given their relatively benign side effect profile, treatment with these agents can be considered in early-onset cases suspected to have both diagnoses.

Other considerations

The diagnosis of a monogenic form of CAA has implications for the patient but also for their families, who may benefit from early involvement of a clinical genetics team. Related individuals should, if they wish, be given access to genetic counselling to explore their choices in a variety of areas including predictive (pre-symptomatic) or diagnostic genetic testing, and reproductive options such as preimplantation genetic diagnosis. They may wish to explore opportunities to connect with other similarly affected families, and to participate in research including pre-symptomatic trials of therapies with the potential for disease modification.[293]

Inflammatory forms of CAA are important to recognize as they can respond to immunosuppressive treatment (usually steroids in the first instance). Although clinically and radiologically relapses following treatment withdrawal are now increasingly reported,[239,252] findings from a series of patients with CAA-related inflammation suggest that early immunosuppressive treatment may both improve the initial disease course and reduce the risk of recurrence.[252]

Finally, there are data suggesting that selective serotonin reuptake inhibitors (SSRI) can be associated with increased recurrent ICH risk,[294-296] although the relationship may reflect confounding influences rather than causation and data specifically for CAA and for younger people are lacking. AHA and ASA ICH guidance recommends reserving use of SSRIs for people with moderate-to-severe depression following ICH, but recognizes there is a paucity of data on risk of ICH for specific SSRI medications and on distinguishing risk profiles between SSRIs and other antidepressants including serotonin-noradrenaline reuptake inhibitors (SNRI).[284]

Discussion

In this review, we provide an overview of diagnoses to consider when assessing patients with early-onset CAA, and suggest an approach to their investigation and management. These unusual forms of CAA provide potential insights into the pathophysiology of vascular amyloid deposition. The observation that a range of different amyloidogenic proteins can be deposited in the vasculature has led to the protein elimination failure hypothesis, which proposes that deposition of insoluble amyloid proteins within the walls of blood vessels is associated with failure of normal perivascular clearance mechanisms.[297] The effectiveness of these systems is thought to be influenced by age and *APOE* genotype and might be additionally challenged by certain protein structures particularly prone to vascular aggregation.[297,298] Examples include: mutations associated with PrP-CAA, which all result in 'anchorless' PrP[297]; *ITM2B* mutations in FBD and FDD, which both produce elongated forms of BRI2 protein of identical length; and *APP* missense mutations associated with severe CAA, most of which fall within a narrow region of the amyloid-β coding domain, between codons 692 and 694.[22] Monogenic forms of CAA might also allow the identification of elusive early disease biomarkers, particularly in pre-symptomatic

mutation carriers, as has been the case in D-CAA. The hypothesized prion mechanism of seeding and spread of iatrogenic CAA may have relevance for the pathogenesis of sporadic amyloid-β CAA, for example in understanding the pre-clinical latency period (analogous to that hypothesized in Alzheimer's disease) and some features of sporadic CAA including frequent spatial clustering of siderosis, microbleeds and ICH. Therefore, despite being rare, improving our understanding of disease processes in early-onset CAA subtypes might provide important mechanistic information for other, more commonly encountered, forms of CAA.

The monogenic forms of CAA also serve to demonstrate the range of clinical phenotypes associated with pathological evidence of CAA; it is striking that only a handful of the genetic forms are associated with ICH, and how this does not always correlate with pathological severity. Of the non-amyloid-β CAAs, only cystatin C and leptomeningeal TTR amyloidosis are clearly associated with ICH, with the latter bearing the closest semblance to the clinical phenotype typically associated with sporadic amyloid-β CAA with prominent (and sometimes exclusive) leptomeningeal involvement. One hypothesis might be that significant anatomical involvement of larger leptomeningeal vessels might predispose to a 'haemorrhagic' phenotype, characterized by symptomatic ICH, convexity subarachnoid haemorrhage, cortical superficial siderosis and transient focal neurological episodes, whereas predominantly cortical involvement might have a more 'cognitive' phenotype, where cerebral microbleeds and white matter changes might be present, but other haemorrhagic features are rare. This is supported by data suggesting that the *APOE* ϵ2 allele is associated with leptomeningeal and haemorrhagic phenotypes, whereas the ϵ4 allele is associated with capillary CAA, cognitive phenotypes and Alzheimer's disease pathology.[42,299-304] However, significant and dominant leptomeningeal involvement can be a feature of *APP* and *PSEN1* mutations,[305] and in other non-amyloid-β disorders including those caused by *ITM2B* mutations. An alternative hypothesis is that certain mutations render the resulting protein more toxic to the cellular components of the cerebral (cortical and leptomeningeal) vasculature, due to structural changes.[306,307] The concept of strains, where proteins with the same amino acid sequence can form multimeric assemblies or seeds with distinct aberrant folds of the monomer subunits, is well recognized in prion biology,[308] and there is some evidence that a similar conformational effect might have relevance to phenotype for other proteins including amyloid-β[309,310]; such that structurally distinct amyloid-β seeds or strains might provide an explanation for the clinical heterogeneity observed within families with the same mutation. Finally, it is important to consider the potential impact of these mutations on other non-vascular functions of a given protein. As an example, amyloid-β might have a physiological role in clotting[311]; it is produced by platelets and can induce their aggregation,[87] and further influences clotting via its interactions with fibrinogen.[312] There is evidence that the Dutch and Iowa *APP* mutations result in altered amyloid-β interactions with fibrinogen and subsequent alterations in clot structure.[313] It is therefore possible that haemorrhage in amyloid-β CAA is a 'two-hit' phenomenon, where vascular amyloid deposition (affecting vessel structural integrity) and clotting perturbation are both necessary. Further work will be needed to explore this and related hypotheses.

Early-onset CAA is an important diagnosis to recognize; these rare forms of CAA require focused investigation and management, and have significant implications for both the affected patient and their families. Improved awareness of these unusual forms of CAA amongst healthcare professionals is essential for facilitating their prompt diagnosis, and understanding their underlying pathophysiology is likely to have implications for our understanding of more common, late-onset, forms of the disease.

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Competing interests

The authors report no competing interests.

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