Cerebrovascular Amyloidosis and Dementia

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Abstract: Cerebrovascular amyloidosis occurs increasingly in older age. The amyloid β (Aβ) protein type of cerebral amyloid angiopathy (CAA) is the most common form of this microangiopathy, evident in virtually all cases of Alzheimer's disease (AD). CAA may range from focal deposits to widespread infiltration of amyloid in walls of perforating and meningeal arteries, capillaries and diffuse perivascular plaques. Prior to their degeneration vascular smooth muscle cells may be sensitised and stimulated by the aggregated amyloid peptide itself and cytokines. Two patterns of CAA namely arteriolar and capillary types have recently been recognized. CAA also occurs in other dementing conditions including Down's syndrome and dementia with Lewy bodies. It is the principal feature of the hereditary amyloid angiopathies such as hereditary cerberal haemorrhage with amyloidosis of the Dutch type and familial British dementia. Varying degrees of CAA have been recorded in early onset familial AD. Mutations in the amyloid precursor protein (APP) gene that lie in codons within the Aβ domain may result in a phenotype characterised by severe CAA, cerebral infarction and white matter disease. The apolipoprotein E ε4 allele is a strong factor in the development of Aβ CAA, which may progress to lobar or intracerebral hemorrhages. At least two different transgenic mice models over-expressing human APP implicate neuronal origin of the Aβ within vascular deposits. CAA may largely develop due to lack of clearance by reduced proteolytic degradation and progressive blockage of the interstitial drainage pathways via the brain vascular routes superimposed by age-related arteriosclerotic changes. Current observations from both sporadic and familial cases suggest CAA to be an independent factor for cognitive impairment and dementia.

INTRODUCTION

Although brain microvascular abnormalities were recognised by Alzheimer and several of his contemporaries [1] it was not until Wilhelm Scholz [2] described the term "drusige entartung" in 1938 that lead to the current exposition and pathogenesis of congophilic or more appropriately cerebral amyloid angiopathy (CAA). Not surprisingly Scholz had acknowledged the destructive nature of this process to cerebral arteries. Current evidence shows age rather than gender, history of hypertension or other vascular disease to be the strongest risk factor for sporadic occurrence of CAA [3]. Attempts to identify genetic aberrations in sporadic CAA patients especially those presenting with cerebral haemorrhage during midlife have not been entirely rewarding [4]. Clinically CAA could manifest as several neurological syndromes, encompassing even seizures that leads to cognitive impairment or dementia [5]. These presumably depend upon the distribution of the accumulated protein within the CNS and the related haemorrhages [6, 7]. However, severe CAA is a high risk for haemorraghic strokes (Fig. **1**).

CAA IN THE AGEING BRAIN AND ALZHEIMER'S DISEASE

CAA may be caused by the aggregation and fibrillisation of one of several proteins enriched in the brain. These include transthyretin, transferrin, cystatin C or gamma trace protein and amyloid β (Aβ). Aβ protein associated CAA that invariably also contains cystatin C is the predominant type of CAA occurring in old age with a prevalence of ~2% in those over the age of 65 years. Autopsy studies of community and hospital cohorts show it is the most common vascular lesion in sporadic Alzheimer's disease (AD). Aβ type of CAA is present in 62-97% of AD and in virtually all Down's syndrome cases [3, 7-10]. Our analysis on isolated cerebral vessels in parallel with brain tissue from a series of over 300 cases indicated that CAA, which varied from focal deposits to more widespread lobar infiltration of the vasculature was apparent in 99% of the AD cases that met the Consortium to Establish a Registry for AD (CERAD) criteria [10-12]. CAA extends in walls of vessels in the leptomeninges, perforating arteries, intraparenchymal arterioles as well as focal deposits in capillaries and perivascular deposits (Fig. **2**). Analysis of isolated cerebral microvessels has further indicated that the longer more toxic peptide Aβ (42) appears to deposit first followed by the Aβ (40) peptide (Kalaria *et al.*, unpublished observations). An abundance of non-fibrillar (soluble) form of Aβ aggregates which are Congo Red negative was also evident [11]. Double immunostained serial tissue sectioning suggested that arteriolar Aβ deposition occurs in the medial-adventitial layers in a circumferential pattern with gradual infiltration of the intimal layers [13]. Electron microscopy has further shown that amyloid aggregates may be found within vascular smooth muscle cells (Fig. **2**) [13]. In AD, CAA was frequent

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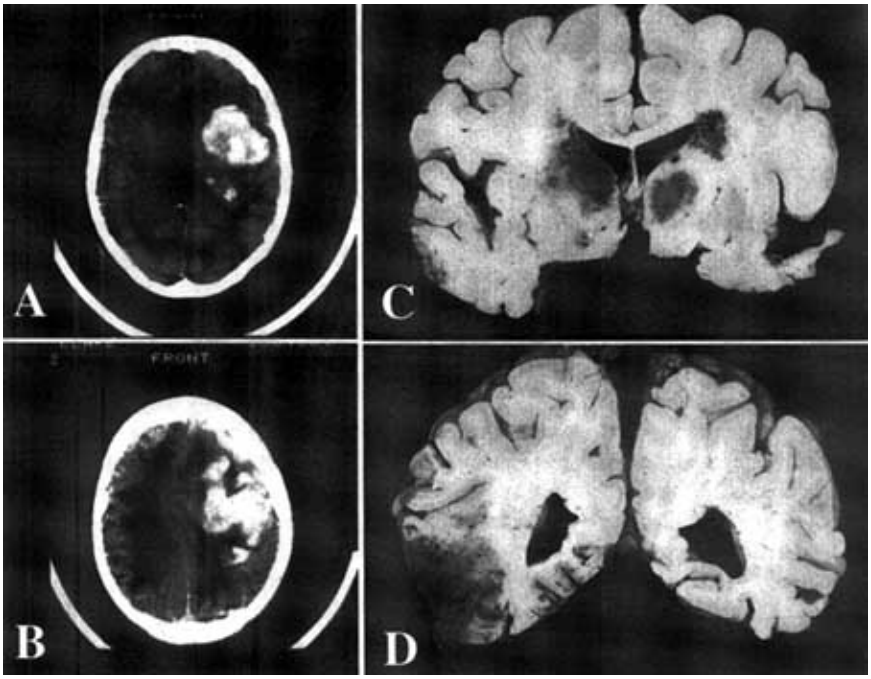

Fig. (1). Imaging and gross pathology in CAA. A, B show serial computed tomography (CT) scans of a 65-year-old woman diagnosed with dementia. She had left temporal involvement caused by a lobar haemorrhage associated with severe CAA. There was general absence of Alzheimer pathology, which did not reach CERAD criteria for possible AD. C, D Coronal slices from a 69-year-old man with CAA-related haemorrhages revealed upon gross examination. Note multiple bleeds bilaterally involving basal ganglia and extending into left occipital lobe. This patients *APOE* genotype was ε4/ε4.

in the occipital lobes and more profound in the sulci compared to the gyri of the neocortex. Intense vascular amyloid may also occur in microvessels within the cerebral white matter (Fig. **2**). In such cases microinfarcts appear to be frequent (Kalaria *et al.*, unpublished observations). Vascular deposits rarely occur in the large cranial arteries or muscular vessels of peripheral organs even in patients with a relatively high degree of cerebral Aβ burden. For example, Aβ deposits are seldom seen in the vessels of the circle of Willis or in the basilar and vertebral arteries. The characteristic cerebral distribution of CAA including lack of profound CAA in non-blood brain barrier vessels within or outside the cranium implicates the process is limited to brain vessels with a tight endothelium and restricted to brain regions bearing the blood-brain barrier (BBB) [14].

Aβ end-terminal specific antibodies and mass spectrometry also showed that vascular amyloid deposits contain mixtures of Aβ(42) and Aβ(40) peptides with the predominance of the latter. Vascular deposits invariably also contain apolipoprotein E, amyloid P component, inflammatory markers including complement and cytokines, and proteoglycans [15]. Sporadic AD cases masking as CAA variants exhibiting largely microvascular lesions have also been described [12, 16]. More recent studies have defined two types of Aβ CAA [17]. Type I CAA involving cortical capillaries, arterioles, venules and even veins (Fig. **2**) was also associated with a high frequency of the apolipoprotein E (*APOE*) -ε4 allele (also see below). Type II CAA was predominantly found in the larger vessels including the leptomeninges and cortical arteries that had higher frequency of the ε2 allele types. Type I CAA did not vary significantly with CAA severity or increasing age suggesting that it is a different entity from type II. However, these differential distributions of Aβ in the vascular wall and perivascular deposits may depend on development of thrombi or lumen occlusion and degree of arteriosclerosis [18, 19]. CAA likely enhances changes in the perivascular nerve plexus or local circuit neurons. Evidence to support this notion is demonstrated by the presence of *tau* positive perivascular cell processes [16] and loss of cholinergic nerve terminals in AD [20].

CAA may result from head injury or indiscriminate haemorrhagic strokes as a consequence of trauma, oxidative stress or haemodynamic stress within brain tissue [21]. There can be little doubt that cerebral vascular amyloid deposition resulting in CAA compounds the ageing related microvascular abnormalities in AD [14]. It is likely that the characteristic vascular deposition in AD along with changes in blood rheology compromise BBB function and promote chronic hypoperfusion [22]. CAA may also lead to functional changes in the cellular elements of the cerebral microvasculature. Thomas *et al.* [23] reported that the interaction of Aβ with endothelial cells of the rat aorta produced excess of superoxide radicals, which caused endothelial damage. The increased superoxide radicals further caused enhanced vasoconstriction by scavenging the endothelium-derived relaxing factor or nitric oxide (NO), and opposing the vasodilator effect of NO. This action may also lead to production of potent oxidizing agents, which may induce lipid peroxidation and other degenerative changes. In accord with this it has been demonstrated in APP over-expressing transgenic mice that products of APP may induce profound and selective impairment in endothelium-dependent

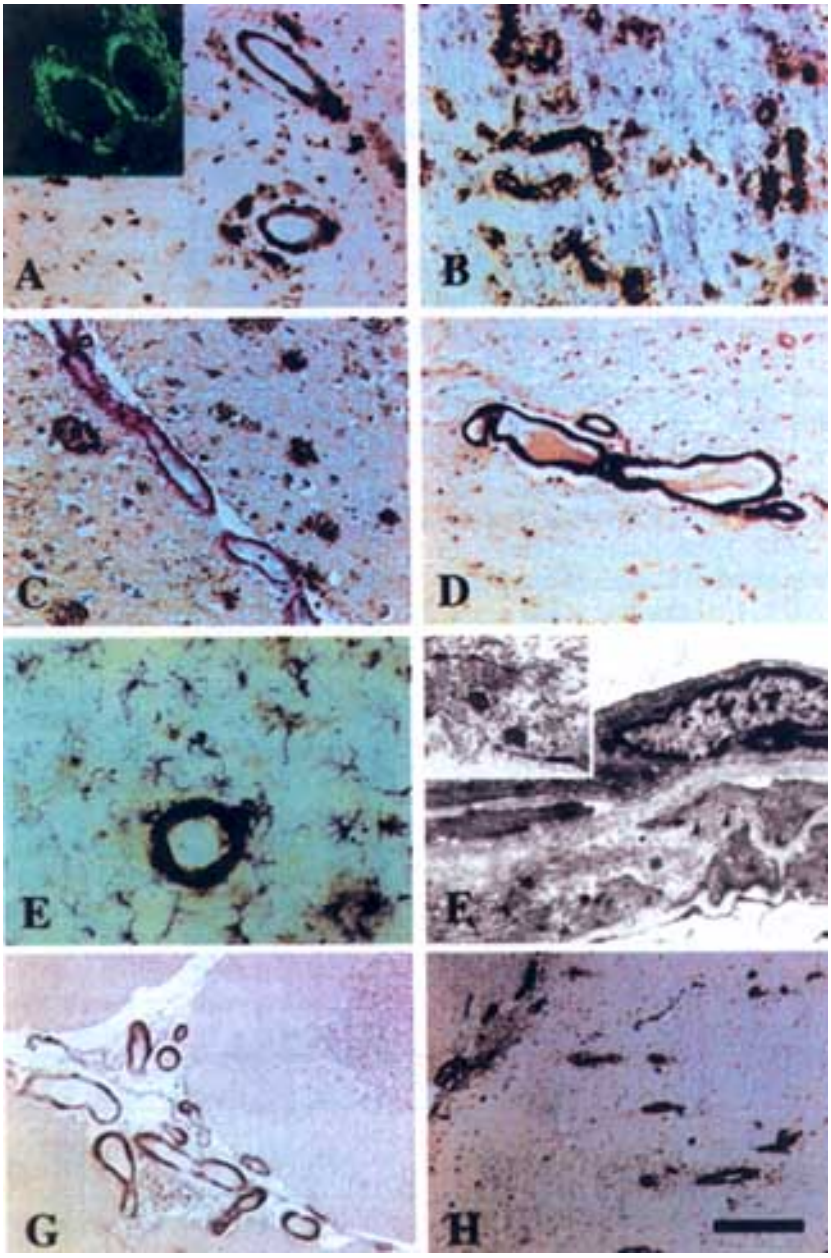

Fig. (2). Neuropathology of CAA in sporadic and familial AD. A, Type II CAA: typical vascular Aβ infiltration in parenchymal arterioles and perivascular diffuse plaques. Inset shows amyloid fibrils in pial vessel walls revealed by Congo red stain, which is evident as apple-green birefringence under polarized light. B, Type I CAA: Aβ deposits involving capillaries in an AD case. C, perivascular plaques with cores in the presence of unaffected intraparenchymal cerebral arteriole (red) in the occipital cortex. D, marked CAA involving a large vessel in the white matter in a subject with mild AD pathology. E, HLA-DR positive microglia localized around a cerebral vessel with amyloid in an AD case. F, electron microscopy reveals amyloid fibrils associated with smooth muscle cell in an arteriole affected by CAA. Inset shows vesicles (arrow heads) associated with the plasma membrane (Courtesy of G. Perry, CWRU). G, Severe CAA in cerebellar pial vessels stained by antibodies to Aβ(42) in an early onset AD subject with the Swedish double mutation. Cerebellar vessels are found to be consistently affected in familial AD subjects. H, Aβ microangiopathy in the occipital lobe of a 20-year-old Squirrel monkey (*Samiri cerius)*. Magnification bar: 100 μm for A-E, G and H. EM (F) magnification X 20,000.

regulation of the neocortical microcirculation [24]. However, such endothelial dysfunction was not evident upon application of the oxygen-radical scavenging enzyme superoxide dismutase in the mice. The activity of the enzyme, nitric oxide synthase (NOS) responsible for NO synthesis has also been reported to be elevated in brain microvessels of patients with AD also exhibiting CAA [25]. This may indicate an increased production of NO as a compensatory mechanism in the cerebral microcirculation in the dementia patients. As NO may also have neurotoxic effects, it has been suggested that increased production of NO could contribute to local neuronal damage. Thus the direct actions of Aβ peptides on the endothelium or that mediated via the smooth muscle cells may bear detrimental effects on local perfusion and cerebral blood flow.

CAA may co-exist with other neurodegenerative disorders. Widespread Aβ form of CAA has been reported to occur in sporadic Creutzfeldt-Jakob disease [26, 27]. Extensive CAA and lack of severe spongiform change had obscured the pathological diagnosis in a 73-year-old man suspected of Creutzfeldt-Jakob disease [27]. These findings suggest the prion protein aggregation or accumulation may impact on the metabolism or clearance of Aβ via the vascular drainage pathways. Interestingly, several reports have confirmed the co-localisation of CAA with forms of angiitis [28-31] suggesting that inflammatory mechanisms are intimately involved in vascular amyloid accumulation. CAA is found to occur with other unrelated pathologies [32] but perhaps not surprisingly it is linked to cerebral infarctions [33, 34]. CAA is also considered a strong risk factor for cerebral ischemia. CAA but not Aβ plaque formation was found to be significantly more common in patients with ischemic cerebral infarction than in age-matched controls with non-vascular lesions [33]. Furthermore, severity of CAA was associated with an increased frequency of cerebral infarction in patients with AD [34]. Ischaemic white matter lesions associated with lipohyalinosis and narrowing of the lumen of the small perforating arteries and arterioles, which nourish the deep white matter, often occur in AD and are common in vascular dementia [35, 36]. Upon magnetic resonance imaging (MRI) these correspond best with deep white matter hyperintensities, which may be evident in more than 60% of AD patients [36]. The relationship between white matter lesions and CAA has also been explored in AD cases without significant vascular pathology [37, 38]. Using a quantitative scale for grading the lesions Haglund and Englund [38] reported that the degree of CAA was correlated with the degree of white matter pathology. Although this report is at variance with previous studies possibly due to different grading and staining methods it is interesting that similar conclusions have been reached in clinical studies. Few studies have suggested CAA to be associated with extensive diffuse hyperintensities presenting as multifocal non-haemorrhagic leukoariosis [39]. The presence of CAA in these cases was proven by biopsy [39].

CAA is considered an important cause of brain haemorrhages. Lobar and intracerebral haemorrhages as opposed to subarachnoid bleeds are common (Fig. **1**). Intracerebral haemorrhages invariably involve subcortical structures rather than cortical layers [10, 34, 40]. Autopsy surveys suggest that 10-15% of the severe CAA cases bleed. We have noted that up to 10% of AD subjects exhibit CAA related intracerebral haemorrhages [10]. The Honolulu Asia Aging study also confirmed that CAA was associated with both small and large haemorrahges [6] and reported that CAA was associated with lower concentrations of Aβ(42) in the cerebrospinal fluid (CSF) [41]. This may explain why high concentrations of Aβ peptides are retained by cerebral vessels [14]. Interestingly, AD subjects with evidence of intracerebral haemorrhage were found to exhibit higher proportions of the longer pathogenic Aβ(42) peptide compared to more soluble Aβ(40) in the vasculature (Fig. **3**). Whereas intracerebral bleeds characterise the Dutch and Flemish variants of cerebral haemorrhage with amyloidosis, it may cause premature death in the elderly and AD patients. Using serial sections from CAA-related haemorrhagic stroke cases Yamada and colleagues [42] have proposed a mechanism how haemorrhages may occur subsequent to initial amyloid deposition (Table **1**).

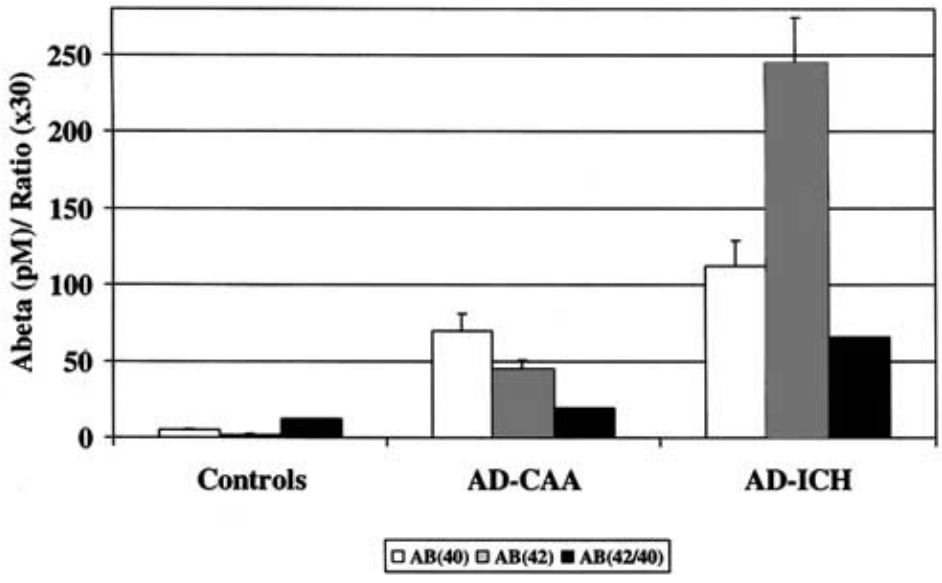

Fig. (3). Aβ peptides in cerebral microvessels isolated from cerebral cortex of AD subjects with moderate CAA (AD-CAA) and severe CAA with intracerebral haemorrhage (AD-ICH). Cerebral microvessels from all AD subjects had significantly more Aβ(40) and Aβ(42) peptides compared to age-matched normal controls. However, microvessels from the AD-ICH subjects had greater Aβ(42)/Aβ(40) ratios compared to the AD-CAA subjects. Age range 60-80 years for n= 5-7 in each group (Kalaria *et al*, unpublished results). These observations suggest increased Aβ (42) accumulation in the vessel walls precedes CAA-related cerebral haemorrhage.

Table 1. Putative Vascular Changes Prior to CAA-Related Intracerebral Haemorrhage

Change(s)	Proteins and factors
Age related changes and expression of vascular function modifying factors in cerebral endothelium and vascular smooth muscle cells	↑ heme oxygenase- 1, ↑ vascular endothelial growth factor(s)
Dilation of cerebral microvessels	↑ nitric oxide synthase (NOS) type 3
Accumulation of Aβ peptides and aggregates in medial and adventia of vessel walls	↑ cytokines and Aβ peptides
Increased fibrosis and hyalinosis of vessel wall	↑ fibroinectin, proteoglycans and collagens
Perivascular microinfarction and intimal thickening	
Degeneration of vascular smooth muscle cells and loss of wall integrity	↓ metalloproteinases
Rupture of the vessel wall giving way to bleeds	hemosiderin

* Information compiled from several sources [references 42 and 43, and Kalaria *et al*, unpublished observations].

HEREDITARY CNS OR CEREBRAL AMYLOID ANGIOPATHIES

Familial forms of CAA resulting in ischaemic and haemorrhagic infarcts or oligaemia are perhaps the most studied among the hereditary cerebrovascular disorders [43]. It is difficult to estimate their prevalence but more than 100 families with hereditary CAA exist worldwide. The age of onset of hereditary CAA is manifest almost three decades earlier compared to sporadic ageing-related CAA. The clinical picture in these comprises focal neurological signs including spasticity, ataxia, facial paralysis and cognitive impairment often leading to dementia. [44-50]. Consideration of the hereditary cerebral haemorrhage with amyloidosis of the Dutch type (HCHWA-D) disease provides certain clues to a link between CAA and stroke. It is thought that the first stroke-like episode triggers multiple cerebral bleeds which may be preceded by diffuse white matter changes that in turn lead to rapid decline of cognitive functions [51, 52]. Most recent studies using morphometry and semi-quantitative methods showed that the amount of CAA was strongly correlated with the presence or absence of dementia while this was not true for diffuse plaques or neurofibrillary tangles. This strongly suggested that CAA alone causes dementia in the HCHWA-D [52]; a concept likely to be the case in other hereditary amyloid angiopathies. However, cognitive impairment is also a consistent feature in sporadic CAA cases in the absence of other pathologies as verified by neuroimaging and neuropathological assessment [5].

Like in sporadic CAA familial forms may exhibit complete infiltration of meningeal and intracortical microvessels of all sizes but also extend into the cerebellum (Fig. **1**) and spinal cord [43, 64]. A characteristic feature of some of the familial angiopathies is the occurrence of vascocentric plaques [53] that is reminiscent of the type II CAA described in sporadic cases. The vascular deposits may contain heterogeneous mixtures of both mutant and wild type peptides cleaved from the original protein [54, 55]. Almost all the CAA precursor proteins and their mRNAs are abundantly expressed in brain. CSF/serum ratios of the products are relatively large indicating that the amyloid protein originates in the CNS rather than from the circulation as typical of most amyloidosis. Investigation of hereditary CAAs has undoubtedly lead to a better understanding of several novel genes and their products.

Familial CAAs have been linked to cystatin C or γ-trace protein [56, 57], amyloid precursor protein [46, 58-61], gelsolin [48, 62-64], tranthyretin [65, 66] and prion protein [67]. The most recent additions to these are the novel gene *BRI* [68, 69] mutations which cause a familial CAA originally described by Worster-Drought [49]. Aβ associated CAA is the most intensely studied of all the familial CAAs in view of its relationship with Alzheimer's disease. It occurs in Dutch, Flemish, Italian and Arctic kindreds as an autosomal dominant condition segregating with single missense mutations in the Aβ domain of the amyloid precursor protein gene (*APP 770*) at codons 692 and 693 (Table **2**). The Italian and Arctic mutations also occurring in codon 693 are different substitutions than in Dutch patients but all the phenotypes of these 'hot spot' variants clearly implicate that when the genetic defect lies within the Aβ domain (residues 1-40) of APP there is significant cerebrovascular pathology. This rather intriguing effect of the substitutions remains to be elucidated. Some of the first transgenic mice models bearing the Dutch and Flemish mutations [70] (Table **3**) have not thrown much light on this issue but more recently developed transgenic mice may advance understanding of the pathogenetic mechanisms involved in these disorders [Jucker M, personal communication]. Remarkably, however, the Dutch mutant peptide *APP* E693Q exhibits the highest content of beta-sheet conformation and fastest aggregation properties compared to the wild type peptide [71] and other mutants at the same codon. Thus different amino acid substitutions at position 22 of Aβ accord distinct structural properties and attribute to the increased fibrillisation of mutant peptide. The profound pathogenic effects of these mutant peptides have been demonstrated in cultured human cerebrovascular smooth muscle cells. Aβ peptides bind and sensitize cell membranes. Interestingly the mutant peptide D23N was shown to be greater than E22Q or A21G peptides compared to wild type Aβ (40 or 42). The actions of the peptides include increased expression of cytoplasmic APP, urokinase-type plasminogen activator (uPA) and uPA receptor, proteolytic breakdown of actin and other cytoskeletal proteins, and cell death

Table 2. Familial Cerebral Amyloid Angiopathies with Cerebral Haemorrhages or Infarction and Dementia[a]

CAA Type	Chromosome	Gene[b]	Mutation	Variant designation	Product (size kDa)	Ref
HCHWA – Icelandic	20	*Cyst C*	A → T codon 68; Glu → Leu at 11 Cys	E68Q; Acys-Q68	ACys (20 kDa))	44, 45
HCHWA – Flemish	21	*APP*	C → G codon 692; Ala → Gly at Aß 21	A692G; Aß-G21	Aß (4 kDa)	47
HCHWA – Dutch Arctic Italian	21	*APP*	G → C codon 693; Glu → Gln at Aß 22 A → G codon 693; Glu → Gly at Aß 22 G → A codon 693; Glu → Lys at Aß 22	E693Q; Aß-Q22 E693G; Aß-G22 E693K; Aß-K22	Aß (4 kDa)	58 60 61
Dementia with CAA – Iowa	21	*APP*	G → A codon 694; Asp → Asn at Aß 23	D694N; Aß-N23	Aß (4 kDa)	59
Finnish Spinal & CAA - Dutch, American, Japanese -Danish, Czech	9	 *Gelsolin* *Gelsolin*	 G → A codon 187; Asn → Asp G → T codon 187; Asp → Tyr	 N187D; AGel-D187 D187Y; Agel-Y187	 AGel (7 kDa)	 62 63, 64
British dementia (Familial BD)	*13*	*BRI*	TGA → AGA codon 267; stop codon → Arg	Stop267R	ABri (4 kDa)	68
Danish CAA (Familial DD)	13	*BRI*	TTTAATTTGT ins between codons 265-266; frame-shift	Stop265	ADan (4 kDa)	69
Meningio and oculo- CAA [c] -Hungarian -Ohio	 18 18	 *TTR* *TTR*	 A → G codon 18; Asn → Gly T → G codon 30; Val → Gly	 N18G; ATTR-G18 V30G; ATTR-G30	 ATTR (10 kDa) ATTR (10 kDa)	 65 66
Prion Protein CAA	11	*PRNP*	TAT → TAG codon 145; Tyr → stop codon	Y145Stop	PrPamy (7.5kDa)	67

[a]Age of onset range form 30 to 55 years. [b] All the genes are expressed in brain, cerebral vessels and choroid plexus. [c] Mutations also reported in American, Dutch and Japanese families. Data compiled from several references. Abbreviations: APP, amyloid precursor protein; BD, British dementia; BRI, British; CAA, cerebral amyloid angiopathy; DD, Danish dementia; HCHWA, hereditary cerebral haemorrhage with amyloidosis of the Dutch type; PrP, prion protein; TTR, transthyretin.

eventually [72, 73]. These Aβ induced alterations in individual smooth muscle cells presumably precede progressive loss of vessel wall integrity with resultant rupture and haemorrhages (Table **1**).

Familial British dementia (FDB) occurring in a large family with over 200 members is the most recently characterised autosomal dominant form of CAA [49, 74]. In this form of CAA vascular and perivascular deposits consist of a highly insoluble 4-kDa peptide (ABri) cleaved from the putative type-II single-spanning transmembrane precursor protein, which is encoded by *BRI* (Table **2**). A single base substitution at the stop codon of *BRI* generates a longer open reading frame resulting in 33 extra nucleotides with a 277-residue precursor instead of the original 266. Mutations in *BRI*, are also associated with a disorder described in nine cases from three generations of a Danish family. Unconventionally termed as Familial Danish dementia, this form of CAA was originally described as heredopathia opthalmo-oto-encephalica, which manifests in cataracts, deafness, ataxia and early onset dementia [50]. Mutational analysis reveals that duplication of 10 nucleotides between codons 265 and 266 occur in the *BRI* gene producing a frame-shift, which again generates a longer precursor protein that releases a highly insoluble amyloid peptide, ADan [69]. As evident in FDB [75] there is wide distribution of ADan also with Aβ and the CAA involves the spinal cord as well as retinal vessels. Other pathologies include a predominance of parenchymal non-fibrillar amyloid plaques, neurofibrillary changes in the hippocampus and ischaemic lesions in the white matter [76].

APOLIPOPROTEIN E, *APOE* GENOTYPE AND AMYLOID ANGIOPATHY

The ε4 allele of the *ApoE* gene is considered to be the most important genetic factor in non-familial AD. The mechanisms underlying the effect of this allele in AD and CAA pathogenesis are being intensively investigated but is far from clear. However, both *in vivo* and *in vitro* evidence suggest the interaction between *ApoE* and Aβ causes peptide conformation conversion and increased cellular toxicity that also pertains to the cerebral vasculature [77-79].

While the *ApoE* genotype appears to have no apparent influence on hereditary CAAs [80] or familial AD caused by mutations in APP, it was interesting to note that mutations in presenilin 1 gene between codons 1 to 200 was associated with presence of significantly greater CAA compared to those at codons beyond 200 [81, 82]. However, the *ApoE* ε4 allele appears a strong independent factor in the development of Aβ CAA [10, 83, 84]. Severity of CAA in sporadic variants without significant Alzheimer pathology is correlated with the presence of the *ApoE*- ε4 allele. The ε4-allele frequency (48%) in AD subjects with moderate to severe CAA was six times higher than those who exhibited mild CAA. In the subjects with severe CAA, the occurrence of an ε4 allele was increased by a factor of 17. This was despite similar neocortical Aβ plaque densities in the

Table 3. Transgenic Mice Expressing Mutant Amyloid Precursor Protein (APP) and CAA

Transgenic mouse line	Details of transgene	Earliest time Aβ deposition	CAA type of pathology	Other pathology	Ref.
PDAPP	APP V717F (hPDGF-β promoter)	5 months	Minimal focal CAA, mainly meningeal	Neither NFT nor neuronal loss. Cholinergic deficits. Some behavioural changes	111, 112
Tg2576	APP KM670/671NL (hPrP promoter)	6 months	Focal CAA, mainly pial vessels in oldest animals.	Neuritic plaques, no NFT, cholinergic deficits, 14-fold increase in Aß(42). Learning and memory impairment at 9-10 months.	113, 114
Tg APP23	APP KM670/671NL (moThy-1 promoter)	6 months	Pronounced CAA in arterioles and capillaries at 16 months.	Local neuronal loss, synaptic abnormalities, microglial activation, microhaemorrhages	115-117
TgCRND8	APP 695 KM670/671NL + V717F (hPrP promoter)	3 months	Marked CAA. Meningeal as well as parenchymal at 5.5 months	Dense core plaques, neuritic pathology, increased Aß(42), impaired learning and cognitive changes	118
Tg APP/Ld	APP V717I (moThy-1 promoter)	<15 months	Profound CAA ranging from focal to circumferential deposits including intraparenchymal vessels. Degeneration of smooth muscle and aneurysms.	Neuritic plaques Aß(42):Aß(40) lower in vessels vs plaques. Smaller branches of MCA showed focal deposits but not main basal brain arteries. CBF and vasodilatory response preserved.	119
TgAPP/Fl and APP/Du	APP A692G, E693Q (moThy-1 promoter)	None at any age	Expected but no amyloid deposition up to 18 months	Glial reactivity, microspongiosis in white matter, apoptotic neurones, behavioural disturbances	70
Tg YAC APP	APP genomic copy	>12 months	Focal CAA associated with moderate Aß deposits.	Several abnormalities in aged YAC mice including atherosclerosis, lipid vacuoles in endothelium and mitochondrial deletion in brain microvessels	120

Summarised from original references (Ref) shown. Abbreviations: APP, amyloid precursor protein; CAA, cerebral amyloid angiopathy; CBF, cerebral blood flow; Du, Dutch, Fl, Flemish; MCA, middle cerebral artery.

advanced and mild CAA groups [10]. More remarkably, the ε4-allele frequency was highly associated with AD subjects exhibiting lobar or intracerebral haemorrhage, all of which had advanced CAA [10, 83]. These observations on the relationship between *ApoE*- ε4 allele, CAA and CAA-related intracerebral haemorrhage were confirmed [85-87], but it was later unexpectedly found that the *ApoE*- ε2 allele also appears a significant factor in the maturation of CAA related haemorrhages and other vascular abnormalities typical of small vessel disease including in perivascular cellular changes and fibroid necrosis [88-91]. In some accord with these observations, *ApoE*- ε4 more than doubles the risk for subarachnoid hemorrhage whereas the ε2 allele increases risk for cerebral infarction and intracerebral hemorrhage [92].

The role of *ApoE* in cerebrovascular disease, which may exhibit some CAA but not associated with AD, however, is not clear [93]. A meta analysis revealed significantly higher *ApoE* ε4 allele frequencies with more than six-fold greater risk in patients diagnosed with ischaemic cerebrovascular disease compared to age and gender-matched controls. These findings suggest a role for *ApoE* genotype in the pathogenesis of cerebrovascular disease [94]. Frisoni *et al*. [95] had previously implicated comparably high *ApoE*- ε4 allele frequencies in cerebrovascular disease associated with dementia but subsequent clinical reports have not confirmed this finding. Indeed, pathologically confirmed studies showed that ε*4* allele frequencies did not differ between Binswanger's disease and other forms of vascular dementia [96]. However, the *ApoE* ε 4-allele frequency may increase the risk of dementia in stroke-survivors and that ε 4 homozygotes exhibit extensive hypoperfusion related to lesions in the deep white matter than those with other genotypes [97]. The latter is, however, not a consistent finding. An interaction between arterial disease and *ApoE* ε4 was similarly indicated by the finding of a nine-fold increase

in cardiac ischaemia in ε4 homozygotes [98] compared to those with ε3. These observations appear in accord with the notion that the ε4 allele or its product may exert its effects in tandem with hypoperfusion. A direct role through pathological alterations in the vascular wall rather than by secondary mechanisms via cardioembolic or thrombotic changes seems viable but a recent epidemiological study implicated that the effect of *ApoE* in dementia is not through atherosclerosis or other vascular disease but yet unknown actions [78, 99].

CAA IN AGEING NON-HUMAN PRIMATES AND TRANSGENIC MOUSE MODELS

Aβ deposition heterogeneity has been described in various species of ageing non-human primates [100-105]. These include Old and New World monkeys comprising chimpanzees, orang-utans, rhesus, squirrel monkeys and marmosets, which have been useful to study the dynamics of amyloid deposition [106]. Aged squirrel monkeys develop severe CAA and widespread micro deposits in the neocortex that also invariably involve microvessels [107]. The CAA is not associated with mutations or significant polymorphisms in either the amyloid precursor protein or the cystatin C gene [57, 107]. AD type of lesions including CAA are similarly evident in the lower primate species including those that belong to the lemur family [108]. Interestingly, the smallest of the lemurian species *microcebus* develops neocortical $A\beta_{42}$ deposits in the first 5 years of its 10-year life span [109]. Moderate to severe Aβ type of CAA has also been demonstrated to occur in several species of aged dogs [107, 109] among other mammals challenged with antigens [110].

A number of transgenic mice models [111-120] have been developed to replicate AD pathology in laboratory animals (Table **3**). While there appears no viable mouse that exhibits both Aβ deposits and neurofibrillary tangles recapitulating AD lesions, several transgenic mice expressing mutant amyloid precursor protein genes develop profound CAA concomitant with vascular smooth muscle degeneration [115-119]. The vascular deposits have shown to be congophilic and fibrillar as well as associated with typical inflammatory markers [116]. There were no apparent qualitative differences in the fibrils derived from the transgenic mouse or brains of subjects with AD. Furthermore, the vascular deposits may contain a mixture of Aβ peptides in the vessel wall. Focal CAA appears to parallel the appearance of Aβ deposits in the hippocampal formation and the neocotical lobes beginning at 5-6 months (Table **3**). It is noteworthy that prominent CAA involving deep vascular wall infiltration even in the neocortex was evident in older mice overexpressing either the double Swedish mutant APP [116] or the London APP717 mutant but both driven by the mouse Thy 1 transcript. The older APP23 animals also exhibited CAA-related spontaneous hemorrhagic strokes (Table **3**), which were worsened by thromolytic treatment with tissue plasminogen activator [121]. That there may be an endogenous conundrum in these mice is indicated by the haemodynamic changes beginning at age 3 months prior to Aβ deposition [122]. Interestingly, these models also show white matter changes and deficits in cholinergic neurone markers [112, 114, 115] (Table **3**). It has been argued that since the transgene was targeted for neuronal expression the Aβ contributing to the CAA is solely derived from neurones although this may in itself trigger Aβ deposition within smooth muscle cells [116, 119, 123]. Nevertheless, these models exhibiting CAA are useful to study the pathogenesis of CAA as illustrated by new technological developments [124] and evaluate the role of CAA in cognitive function.

MECHANISMS IN CAA

The pathogenesis of CAA and its impact on strokes and haemorrhages remains a key question. Study of the familial forms of CAA and relevant transgenic mice models has provided vital clues but the mechanisms are not understood. In familial disease, altered physical properties of the mutant amyloid peptide presumably lead to an imbalance between accumulation and elimination of the peptide from the CNS. While the variable degree of CAA in different angiopathies and sporadic cases may depend upon regional specificity in production and accumulation of the amyloid proteins collective evidence would suggest that vascular amyloid deposits are derived from both extrinsic and intrinsic sources. The transgenic mice models [116, 119] provide reasonable evidence that widespread CAA results from neuronal derived mutant amyloid peptides. Thus, the deposition in the vessel walls may result enroute to elimination of the enhanced Aβ via the lumen or predominantly the interstitial drainage pathways [17]. However, vascular smooth muscle and endothelial cells are also capable of producing amyloid peptides [11] and may be stimulated by inflammatory molecules and cytokines, e.g. interleukin 1β or the amyloid peptide itself [125]. Perivascular microglia, diffuse plaques and the CSF are likely sources of these triggers [126, 127]. On the other hand, Prior and colleagues [128] have also suggested that smooth muscle cells due to differentiation and maturation may take up amyloid peptides, which would accumulate to produce CAA. It now seems apparent that two factors, applied to both familial and sporadic CAA, may play a role in the enhanced accumulation of the amyloid peptides. First, impaired proteolytic mechanisms due to altered cleavage of mutant peptides [129] or age-related loss of key proteases such as nephrilysin [130, 131] may promote and enhance the accretion of readily aggregated amyloid peptides. Second, age-related cerebrovascular atrophy [132] in tandem with reduced vascular tone or pulsation [18] may impede drainage or interstitial exit routes to cause persistent perivascular build up and CAA. This may be particularly enhanced in microvessels near thrombi [18].

Thus cerebrovascular disease per se may be a causal factor in CAA and if so cerebrovascular disease may also lead to cerebral amyloidosis and neurofibrillary pathology of AD. The notion for lack of vascular drainage is also supported by indirect evidence that the Icelandic variant ACys-Q68 is readily found in the lymph nodes [133] and that CAA is not necessarily purged after substantial removal of Aβ plaques upon vaccination [134, 135]. It is plausible that the angiopathy caused by vascular deposition along penetrating arterioles causes severe perivascular ischaemic foci and decreased perfusion in the vascular bed of the end vessels. In an effort to target cerebral amyloidosis leading to CAA therapeutic strategies have been developed. In particular the proteoglycan mimetics may be useful to develop treatments for CAA [136].

CONCLUSIONS

Recent molecular advances and development of transgenic mouse models have lead to the better understanding of both sporadic and familial forms of cerebrovascular amyloidosis. Collective evidence suggests CAA is a substrate for dementia. Both arterial vessels and capillaries are involved in the microangiopathy, which may result from neuronal as well as intrinsic vascular cell mechanisms. Vascular wall cells undergoing age-related changes likely predispose to amyloid accumulation and succumb to degeneration by direct toxicity. New evidence suggests that whereas resistance to protease cleavage of mutant amyloid peptides is likely a crucial factor in the familial angiopathies it would seem that age-related reduction in proteolytic activity is responsible for the amyloid accumulation in AD and sporadic CAA. Age-related changes in the brain vasculature resulting in reduced vascular pulsation and tone are also factors in the lack of clearance of parenchymal and perivascular amyloid. Strategies that reduce aggregation and enhance cleavage or clearance of accumulated amyloid would overcome CAA to improve cerebral perfusion and permeability with benefit to cognitive function.

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