

Insights into the pathogenesis and pathogenicity of cerebral amyloid angiopathy

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1. ABSTRACT

Amyloid-beta (Abeta) cerebral amyloid angiopathy (CAA) affects most Alzheimer's disease (AD) patients and ~30% of otherwise-normal elderly people. $APOE$ epsilon 4 is a major risk factor for CAA in AD. Neurons are probably the source of the vascular Abeta. CAA develops when Abeta is deposited in the vessel walls along or across which it normally passes into the CSF and bloodstream. Vascular deposition is facilitated by factors that increase $A\beta_{40}$: $A\beta_{42}$, impede perivascular passage of Abeta or raise its concentration. The levels of some Abeta-degrading enzymes are reduced in AD patients with CAA. However, angiotensin-converting enzyme activity is increased and may act via angiotensin II to increase transforming growth factor beta1, a potent inducer of ECM synthesis. CAA is a cause of intracerebral haemorrhage and cerebral ischaemic damage. In AD, neuritic degeneration is accentuated around Abeta-laden vessels. Rarely, CAA is associated with angiitis. The balance between parenchymal and cerebrovascular degradation of Abeta, and regulation of perivascular extracellular matrix production, are likely to be key determinants of Abeta distribution and pathogenicity within the brain.

2. INTRODUCTION

The term cerebral amyloid angiopathy (CAA) describes the accumulation of amyloid in the walls of blood vessels in the leptomeninges and parenchyma of the central nervous system (CNS) (Figure 1). By convention, the designation CAA includes not only amyloid angiopathy in the cerebrum but also that involving other parts of the CNS such as the cerebellum. CAA is a manifestation of several familial diseases in which the amyloid is formed by mutant proteins – mutant amyloid- β ($A\beta$), cystatin C, transthyretins, gelsolin, prion protein, ABri and ADan – and also occurs in some forms of familial Alzheimer's disease (AD) in which there is excessive deposition of wild-type $A\beta$ (1, 2). However, much the commonest forms of CAA are caused by cerebrovascular accumulation of $A\beta$ in sporadic AD and in otherwise-normal ageing. It is these last two that will be the focus of the present paper. The reported prevalence of CAA in the elderly and in patients with AD has varied in different post-mortem series. Esiri and Wilcock (3) found CAA in 82% of patients with AD and a just over 30% of brains in other demented and non-demented patients over 60 years of age, and Premkumar *et al* (4) detected CAA in 96% of patients with AD. In our own series, over 90% of patients with AD had CAA (5).

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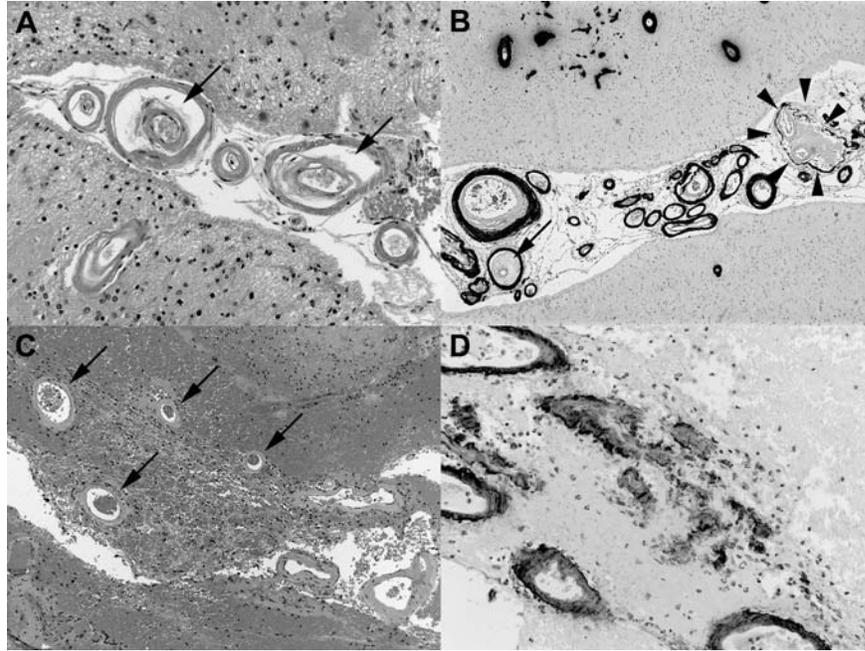


Figure 1. Cerebral amyloid angiopathy (CAA). (A) The tunica media of several leptomeningeal and cortical arterioles has been replaced by homogeneous material. Some of the vessels show concentric splitting of their walls (arrows), due to separation of the amyloid-laden tunica media from the intima. Haematoxylin and eosin. (B) Immunohistochemistry shows the homogeneous material in the tunica media of the leptomeningeal blood vessels to be strongly positive for A β . A β is also present in a cluster of capillaries and small arterioles in the cerebral cortex. The arrow indicates a vessel with marked narrowing of the central lumen, and the arrowheads surround an A β -laden vessel that has undergone previous thrombosis and recanalisation. (C) This section is from the brain of a patient with CAA who had a fatal haemorrhage into the cerebral cortex and subarachnoid space. Note the structureless appearance of many of the blood vessels within the haematoma (arrows), the walls of which have been largely replaced by amyloid. Haematoxylin and eosin. (D) Immunohistochemistry shows A β in the walls of the blood vessels within the haematoma. Some of the blood vessels appear fragmented.

CAA was also present in about 30% of elderly people without AD or other neuropathological abnormalities (6); the proportion rose from 13.8% of people between 60 and 69 years to 44.8% of those 80 years and above.

In this review we summarise current information on the pathogenesis of sporadic CAA, genetic risk factors for this condition, and its clinical and pathological complications.

3. PATHOGENESIS

Over the years there has been much debate as to the origin of the A β in CAA – whether it is derived from neurons in the brain parenchyma, cells in the vessel walls (particularly smooth muscle cells in the tunica media) or systemic tissues (in which case the A β would enter the vessel walls from the bloodstream). There is now overwhelming evidence from transgenic mouse models that neuronal production of A β is sufficient to cause CAA (7-9). As noted below, endothelial receptor for advanced glycation end-products (RAGE) is capable of transporting A β from the bloodstream into brain (10, 11). However, the restricted distribution of CAA, the fact that the cerebrovascular A β first accumulates away from the vessel lumen (in the perivascular extracellular matrix of capillaries and the basement membranes on the abluminal

aspect of the tunica media in arterioles) and the absence of CAA in transgenic mice over-producing A β systemically (12) all argue against a significant contribution of circulating A β to CAA. Isolated cerebral microvessels were reported to synthesise A β (13) and small amounts of A β can be demonstrated within smooth muscle and endothelial cells. However, both smooth muscle (14) and endothelial cells (15-17) are able to internalize exogenous A β , by interactions involving apolipoprotein E (apoE) and the low-density lipoprotein receptor family; the demonstration of A β within these cells does therefore not preclude neuronal origin. It remains possible that cerebrovascular cells may make a small contribution to the production of A β within the CNS but the balance of evidence points to a neuronal origin for most, if not all, of the A β in CAA.

3.1. A β 40 predominates in CAA

In contrast to the A β that accumulates in parenchymal plaques, in which A β 42 is more abundant than A β 40, the latter predominates in CAA (18). Jucker and colleagues (18, 19) conducted a series of elegant experiments, comparing the distribution of A β in APPDutch mice (transgenic for a mutant form of amyloid precursor protein (APP) that leads to overproduction of A β 40 and causes Dutch-type hereditary cerebral haemorrhage with amyloidosis) and in mice with, in

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addition, a G384A mutant presenilin-1 transgene that decreases the ratio of A β 40:42. The results of this and of other studies (reviewed in (18)) showed that the ratio of A β 40:42 plays a key role in determining whether A β accumulates in the brain parenchyma or vasculature. Extracellular A β 42, which is more prone than A β 40 to aggregate and form fibrils, tends to precipitate within the brain parenchyma. A β 40 is probably more likely to reach the blood vessels and therefore to accumulate within the vascular and perivascular extracellular matrix (ECM).

3.2. Relationship between synthesis and accumulation of A β in sporadic CAA

Cerebrovascular accumulation of A β can be caused by excessive neuronal synthesis of A β 40 (as in Dutch-type hereditary cerebral haemorrhage with amyloidosis), an increase in the overall level of A β production (e.g. in trisomy 21 (20, 21) or in families with duplication of the APP locus on chromosome 21 (22, 23)) or an increase in the ratio of A β 40:42, as noted above. The ratio of A β 40:42 may be influenced by *APOE* genotype (see below), a well established risk factor for CAA (4, 5). To date there is, however, little documented evidence to suggest that an increase in neuronal synthesis of A β 40 or in the overall level of A β production is primarily responsible for the development of sporadic CAA.

Tyler *et al* (24) reported that homogenates of temporal cortex from AD patients showed an increase over controls in the activity of β -secretase-1 (BACE-1), the rate-limiting enzyme in A β synthesis, and a decrease in the activity of α -secretase, which prevents the formation of A β . Several other groups also found BACE-1 activity (but not always protein level) to be elevated in AD (for review see (25)). Stockley *et al* (26) showed that the increase in BACE-1 activity in AD was due to a rise in the maximum rate of activity of this enzyme; in their study, the concentration of BACE-1 was reduced in AD, particularly in cases with more advanced disease, indicating that a post-translational mechanism was responsible for increasing BACE-1 activity. To try to establish whether or not increased BACE-1 has a primary role in A β accumulation in AD, Zhao *et al* (27) analysed the timing of changes in the expression of this enzyme in two mouse lines transgenic for mutant APP – one with early and one with late accumulation of A β . In both mouse lines BACE1 protein increased only after commencement of A β plaque formation. The increase occurred around the plaques and without any change in BACE1 mRNA level, implicating a post-transcriptional mechanism. It seems therefore likely that changes in the synthesis and activity of BACE1 are secondary to A β accumulation or some other related pathological process in AD. Although these findings argue against a primary role for increased BACE1 activity in the formation of plaques or development of CAA, a positive-feedback loop initiated by parenchymal accumulation of A β could nonetheless exacerbate A β production and the development of CAA.

3.3. Perivascular clearance of A β

Unlike most other tissues, the brain does contain lymphatic vessels. At least in the rat, interstitial fluid in the

white matter spreads widely and appears to drain into the ventricular cerebrospinal fluid (CSF) (28). The drainage differs for the cerebral grey matter, from which injected tracers pass along cortical blood vessels to the pial surface of the brain and into the CSF in the subarachnoid space (28, 29). The precise route of drainage along the cortical blood vessels depends on the size and properties of the tracer; particulate tracers such as Indian ink fill perivascular spaces (30) whereas soluble dextran spreads along capillary and arteriolar basement membranes (29). From both locations tracer is also taken up by perivascular cells (30). Mathematical modelling suggests that arteriolar pulsation could provide the propulsive force needed to drive fluid in perivascular spaces in reverse direction to the arterial blood flow (31).

The perivascular, predominantly periarteriolar distribution of A β in the cerebral cortex in CAA closely resembles that of tracers shortly after their injection into the grey matter of rats (32). It seems likely that soluble A β reaches CSF in the subarachnoid space by periarteriolar drainage, as proposed by Weller and colleagues (32-34), and that CAA occurs when some A β precipitates out of solution and is deposited in the walls of the arterioles along which it drains. The likelihood of precipitation may be increased by factors that increase the concentration or affect the composition of perivascular A β or that impede its drainage into the CSF. Circumstantial evidence for the latter came from the observation (made on examination of serial histological sections cut tangential to the pial surface) that capillary beds distal to cortical arterioles occluded by thrombus were more likely than other capillary beds to show accumulation of A β (35). Thrombosis would interfere with arteriolar pulsation and this, by impeding the drainage of A β -containing fluid along the surrounding periarteriolar space, presumably promoted the deposition of A β around capillaries.

3.4. Transport of A β from brain into blood

Some soluble A β is removed from the brain by transport across vessel walls, into the circulation. At least in part, this transport involves the binding of A β to low-density lipoprotein receptor-related protein-1 (LRP-1), as evidenced by the observation that the elimination of radiolabelled soluble A β from mouse or rat brain is significantly reduced by prior administration of receptor-associated protein or antibodies to LRP-1 (16, 17) or by deletion of the receptor-associated protein gene (15). A β 40 is cleared more rapidly than A β 42 through this pathway but the clearance of A β 42 can be enhanced by its binding to ApoJ (36). LRP-1 is expressed by brain capillary endothelial cells (16, 17, 37). Outside of the CNS, LRP-1 is also strongly expressed by vascular smooth muscle cells (38) but whether this is also the case in the brain has not been specifically examined. LRP-mediated transport of A β across the mouse blood-brain barrier is reduced by polymerisation of the A β to form fibrils (15). Donahue *et al* (37) reported a reduction in microvascular LRP-1 in AD. It is not clear from their analysis whether or not this reduction was related to the presence of CAA

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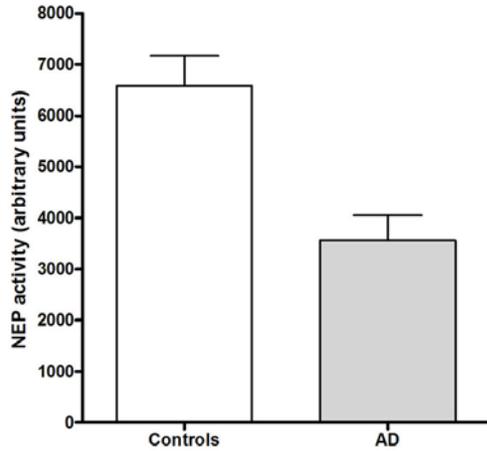


Figure 2. Neprilysin (NEP) activity in Alzheimer's disease (AD). (A) NEP activity is significantly in frontal cortex from AD compared with control brains ($p < 0.01$). The assays were repeated on 3 separate occasions. Bars show mean values and standard error of mean for 16 Alzheimer disease cases and 16 controls. Reproduced with permission from the Journal of Neuropathology and Experimental Neuropathology (55).

3.5. RAGE-mediated transport of A β into the brain

Experimental studies indicate the potential for transport of A β from the blood into the brain, through the binding of circulating A β to receptor for advanced glycation end-products (RAGE) in endothelial cells (10, 11). The concentration of A β in the circulation is much lower than that in the brain and it is unclear to what extent this pathway contributes to the cerebrovascular accumulation of A β in man. Donahue *et al* (37) reported strong microvascular immunopositivity for RAGE in AD, although labelling of neurons for RAGE was reduced. The binding of systemically infused A β to RAGE-bearing cells in the vessel walls led to upregulation of endothelin-1 (11). This is of possible relevance to our own observation of increased microvascular expression of endothelin converting enzyme-1 (ECE-1) in AD (see below).

3.6. Transforming growth factor β 1, perivascular ECM and CAA

The transforming growth factor β (TGF β) family of cytokines comprises several homologous polypeptides that transduce a range of signals involved in cell growth and differentiation, and the response to inflammation and tissue damage. The family members TGF β 1-3 are present in all mammalian tissues, including the CNS, and are potent inducers of the synthesis of collagen and other components of the ECM. Immunohistochemical studies showed TGF β 1 and TGF β 2 to be present in plaques and NFTs in AD (39, 40), and the concentration of TGF β was elevated in cerebrospinal fluid and serum of patients with AD compared to controls (41). TGF β 1 immunoreactivity was increased and levels of TGF β 1 mRNA in the midfrontal cortex were three-fold higher in the frontal cortex of AD than control brains (42). Transgenic mice with over-expression of TGF β 1 by either astrocytes (42, 43) or neurons (44) accumulated increased ECM perivascularly

and developed CAA. In human cerebral cortex, the severity of CAA correlated directly with TGF β mRNA levels (42). In addition, whereas mice over-expressing APP showed only parenchymal accumulation of A β , combined over-expression of APP and TGF β 1 resulted in early and extensive CAA (42).

TGF β 1-mediated up-regulation of perivascular ECM may cause CAA by impeding clearance of A β , both along periarteriolar drainage pathways into the CSF and across blood vessel walls into the circulation. It has also been suggested that TGF β -induced activation of microglia may promote the break-up of A β plaques by phagocytosis (45) and this could, in theory, increase the delivery of A β to cerebral blood vessels, in a manner analogous to that proposed to account for the severe CAA in A β -related angiitis (46) and in some patients who were immunised with A β (47-49).

3.7. Several A β -degrading enzymes are present in the cerebral microvasculature and are deficient or less active in AD and CAA

Neprilysin (NEP) is a neutral zinc metallo-endopeptidase that can hydrolyze A β 40 and A β 42, both *in vitro* and *in vivo* (50, 51). It cleaves monomeric and oligomeric forms of A β 40 and A β 42 (52) but not the abnormal forms of A β that result from the Dutch, Flemish, Italian or Arctic mutations in APP (53). Inactivation of the NEP genes in mice caused elevation of the levels of A β 40 and A β 42 in the brain and plasma, prolongation of the half-life of soluble A β in the brain, and increase in the hippocampal A β plaque load and the development of CAA (54). In human cerebral cortex, we (55) and others (56) showed NEP to be most abundant in pyramidal neurons and in smooth muscle cells in the tunica media of blood vessels. Immunohistochemistry revealed a reduction of vascular and parenchymal NEP in AD (Figures 2 and 3). The loss of vessel-associated NEP was inversely related to the severity of CAA. Analysis of cases with severe CAA showed that levels of vascular NEP were reduced to the same extent in A β -free and A β -laden vessels, suggesting that the reduction in NEP was not secondary to CAA but may have contributed to its development (55). Possession of APOE ϵ 4, a genetic risk factor for CAA (see below) was associated with significantly lower levels of both parenchymal and vascular NEP. Co-linearity of ϵ 4 with the presence of moderate to severe CAA precluded assessment of the independence of this association from NEP levels. However, logistic regression analysis showed low NEP levels to be a significant independent predictor of moderate to severe CAA.(55).

Endothelin-converting enzyme (ECE)-2 also degrades A β , is present in the cerebral microvasculature and is deficient in CAA. ECE-1 and -2 are homologous enzymes that belong to the same family of zinc metallo-endopeptidases as NEP (57, 58). Mice lacking ECE-2 have increased levels of A β 40 and A β 42 in the brain. We have found ECE-2 to be present in pyramidal neurons in the human cerebral cortex and also, albeit at lower levels, in smooth muscle cells of the tunica media. Like NEP, expression of ECE-2 is reduced in AD (59). Whether

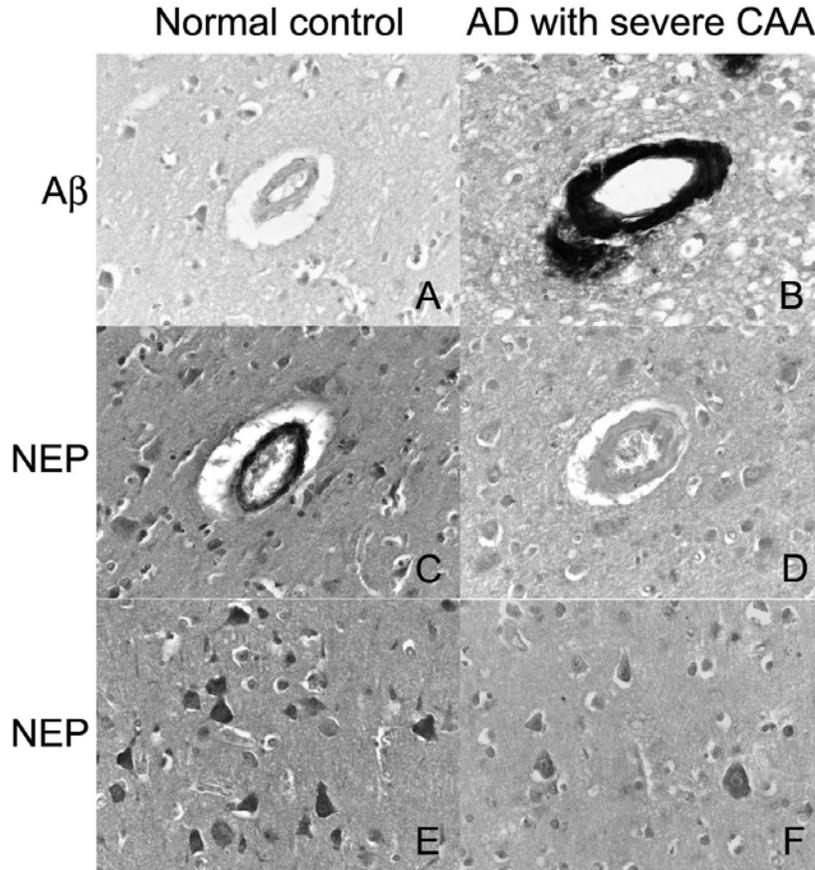


Fig Figure 3. Immunoperoxidase labelling of A β and NEP within the neocortex. In a control case with no CAA, there is no demonstrable A β (A), but abundant NEP in the tunica media of cortical blood vessels (C) and in the surrounding cortex, particularly in pyramidal neurons (E). In contrast, sections from a patient with AD and severe CAA show vascular accumulation of A β (B), but no detectable vessel-associated NEP (D) and only scanty NEP within pyramidal neurons (F). Reproduced with permission from the Journal of Neuropathology and Experimental Neuropathology (55).

changes in the cerebrovascular expression of ECE-2 are causally related to the development of CAA has yet to be determined but the loss of tunica media in severe CAA seems likely to reduce the capacity for local degradation of A β and thus to increase its accumulation in vessel walls.

Insulin-degrading enzyme (IDE) is another enzyme that is capable of degrading A β , including the A21G (Flemish), E22Q (Dutch) and E22K (Italian) variants (60). Sequence variants in the IDE gene were reported to be associated with AD and A β parenchymal load (61-63). IDE is expressed by cultured human brain endothelial cells (60) and isolated microvessels (64). IDE protein levels were increased in microvessels from AD patients with CAA but the enzyme activity of IDE was significantly reduced in CAA in comparison with controls (64).

3.8. Cerebrovascular ECE-1 is increased in AD

As noted above, ECE-1 is a member of the same family of endopeptidases as NEP. It cleaves A β 40 and A β 42 at multiple sites *in vitro* (58), and heterozygous inactivation of the *ECE1* gene increases the levels of A β 40 and A β 42 in the mouse brain *in vivo* (65, 66). Within

human cerebral cortex, we have found specific immunolabelling of ECE-1 to be most abundant in the endothelium and the level of ECE-1 mRNA to be elevated in AD. Deane *et al* (11) reported that systemic infusion of A β in mice caused RAGE-mediated uptake of the A β by cerebral microvessels and their synthesis of endothelin-1 (ET-1). Conversion of the 38-residue proenzyme to the 21-residue vasoconstrictor peptide ET-1 is mediated by ECE-1 (67). Synthesis of ET-1 in response to the binding of A β to RAGE may therefore be a consequence of upregulation of endothelial ECE-1 by A β . This upregulation could, at least theoretically, also protect against the deposition of A β , particularly within the intima.

3.9. Involvement of other A β -degrading enzymes in AD and CAA

The possible role of other A β -degrading enzymes in AD and CAA is still unclear. Angiotensin-converting enzyme-1 (ACE-1) is capable of cleaving both A β 40 and A β 42 *in vitro* (68-70), and several studies, including a large meta-analysis, demonstrated a significant association between an insertion/deletion polymorphism in the angiotensin 1-converting enzyme (*ACE*) gene and AD in

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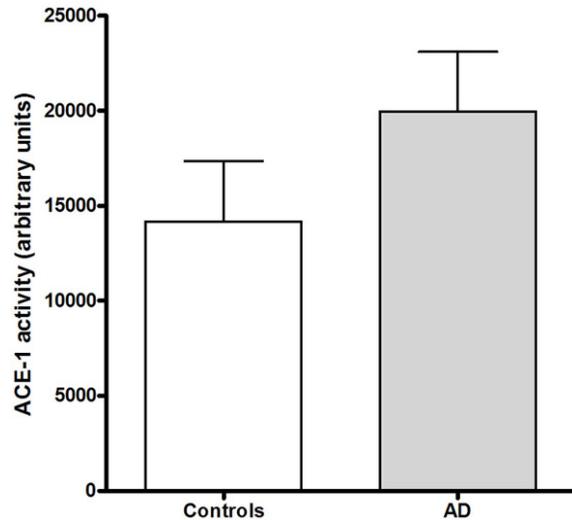


Figure 4. Angiotensin-converting enzyme-1 (ACE-1) activity in homogenates of frontal cortex (Brodmann area BA6) in AD and control brains. Bars show mean values and standard error of mean. The difference between AD cases and controls is statistically significant ($p < 0.001$). Reproduced from (74).

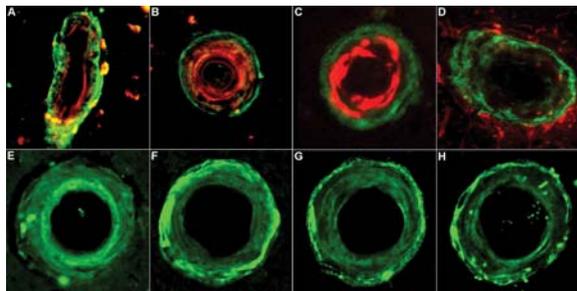


Figure 5. Immunofluorescent labelling of ACE-1 and other markers of cells and tissues in and adjacent to the vessel wall. (A-D) These images are of sections double immunofluorescently labelled for ACE-1 (green) and vimentin (red, in A), collagen IV (red, in B), smooth muscle actin (red, in C) or glial fibrillary acidic protein (red, in D): there is no colocalisation of ACE-1 with any of the other antigens. (E-H) These images are of serial sections through the same arteriole, immunofluorescently stained for laminin (E), decorin (F), fibronectin (G) and ACE-1 (H): the distribution of ACE-1 (H) within the vessel wall differs from that of laminin (E) but is very similar to that of decorin (F) and fibronectin (G). Reproduced from (74).

diverse populations (61, 71, 72). However, Lendon *et al* (73) found no association between *ACE* genotype and either $A\beta$ load or severity of CAA, and in a short-term study in mice, Eckman *et al* (66) found that ACE inactivation or inhibition did not alter $A\beta$ concentration in the brain. We found ACE-1 activity to be increased in AD (Figure 4), in direct relationship to parenchymal $A\beta$ load (74). ACE-1 accumulated in the perivascular ECM, particularly around cerebrocortical blood vessels with

accumulation of $A\beta$ (Figure 5). The possible significance of this perivascular upregulation of ACE-1 remains to be determined.

Matrix metalloproteinases (MMPs) are zinc- and calcium-dependent endopeptidases, several of which are produced by neurons and glial cells in the nervous system. MMP-2, -3 and -9 are all capable of cleaving $A\beta$ peptides (75-78) and MMP activity was reported to be increased in the hippocampus in AD (79). However, we found no significant difference between AD and control brains when we measured the levels and activities of MMP-2, -3 and -9 in frontal cortex (80). Furthermore, within the AD cohort, the levels and activities of these MMPs were not related to $A\beta$ load.

Plasmin is a further enzyme that is present in the brain and capable of degrading $A\beta$ *in vitro* (81, 82) and probably *in vivo* (83). Ledesma *et al* (82) found that plasmin levels were reduced in brain tissue from patients with AD but the distribution of the enzyme within the brain and the relevance of this reduction to the development of CAA are currently not known.

4. GENETIC RISK FACTORS FOR CAA

4.1. *APOE* $\epsilon 4$ is associated with CAA, particularly in patients with AD and cerebral haemorrhage

In two large post-mortem series of patients with AD, the presence of CAA was strongly associated with possession of $\epsilon 4$ and the severity of CAA directly related to the number of $\epsilon 4$ alleles (4, 5). An association between $\epsilon 4$ and CAA was also demonstrated in mixed cohorts of elderly patients, including some whose brains included many plaques or had CAA-associated haemorrhage (84, 85). In a mixed cohort of CAA cases which included 16 with and 28 without AD, Thal *et al* (86) found $\epsilon 4$ to be associated with CAA that affected cerebrocortical capillaries and $\epsilon 2$ with CAA that did not involve capillaries. The influence of *APOE* genotype on the development of CAA may be mediated through several mechanisms. Fryer *et al* (87) produced evidence suggesting that one way in which $\epsilon 4$ promotes the development of CAA is through increasing the ratio of $A\beta 40:A\beta 42$. These researchers crossed human $\epsilon 3$ and $\epsilon 4$ knock-in mice with tg2576 mice. The latter are transgenic for APP carrying the Swedish double mutation (K670N and M671L) and develop $A\beta$ plaques as well as CAA. Expression of $\epsilon 4$ by the tg2576 mice increased the ratio of $A\beta 40:A\beta 42$ and largely prevented the formation of plaques but caused the development of severe CAA. Expression of $\epsilon 3$ by the tg2576 mice reduced the ratio of $A\beta 40:A\beta 42$ and led to the formation of only sparse plaques and no CAA. It was unclear from this study whether the increased ratio of $A\beta 40:A\beta 42$ in mice with $\epsilon 4$ was due to an effect on $A\beta$ synthesis, degradation, or clearance into the blood or CSF. One piece of evidence suggesting that $\epsilon 4$ may influence the degradation of $A\beta$ came from the work of Miners *et al* (55) who showed that $\epsilon 4$ was associated with reduced cerebrovascular NEP in AD and elderly control brains and that a low NEP level was a significant independent predictor of moderate to severe CAA.

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It should be noted that $\epsilon 4$ is not associated with CAA in all populations. Most series demonstrating an association between $\epsilon 4$ and CAA have been in Caucasian patients with AD or AD-like changes or with cerebral haemorrhage. Several studies have shown that $\epsilon 4$ is not a significant risk factor for CAA in elderly Japanese (88-90). When we examined the prevalence of CAA in brains from a United Kingdom cohort of 152 people aged 60-102 years, without significant neuropathological changes of AD (i.e. of Braak tange stage II or less) and without cerebral haemorrhage, no association was evident with *APOE* genotype (6).

APOE genotype probably influences the risk of CAA-related intracerebral haemorrhage (ICH) (see below for further discussion of this complication of CAA). In a small number of clinical series, ICH attributable to CAA (i.e. lobar haemorrhage, particularly if multiple or recurrent) was associated with an increased frequency of $\epsilon 4$ (91, 92) although the increase was not always significant (93). $\epsilon 4$ was associated with CAA-related ICH in the post-mortem series of Greenberg *et al* (94) but not the series of Nicoll *et al* (95). The discrepancy may relate, at least partly, to differences in the proportion of cases with AD-like changes in the two cohorts. There was agreement that $\epsilon 2$ was a risk factor for CAA-related ICH (95, 96), possibly because this allele was associated with CAA-related vasculopathic abnormalities – fibrinoid necrosis (97) or cracking of the vessel wall and leakage of blood (96). The interpretation of these post-mortem series is complicated by the influence of *APOE* genotype on survival after ICH. Possession of $\epsilon 4$ was found to be associated with increased mortality after subarachnoid (98, 99) or parenchymal brain haemorrhage (100, 101). Thus the analysis of apparent association between $\epsilon 4$ and CAA-related haemorrhage in post-mortem series may have been skewed by an $\epsilon 4$ -related reduction in survival.

4.2. Other genetic risk factors for CAA

Sequence variations in multiple candidate genes have been associated with CAA in individual series but the associations have generally been weak and have not (as yet) been replicated. These include an association between the severity of CAA and the T/C polymorphism at codon 10 in exon 1 of *TGF β 1* (102), a GT repeat polymorphism in the enhancer/promoter region of *NEP* (103) and polymorphisms in the 5'-region and exon 3 of *LRPI* (104). We found no association between polymorphisms in the *APOE* promoter, *ACE* and *CYP46* genes and the presence or severity of CAA (105).

5. PATHOGENICITY OF CAA

5.1. CAA increases the risk of cerebral haemorrhage

An association between CAA and ICH has been documented in numerous case reports and post-mortem studies (88, 106-112). Haematomas that are multiple or recurrent, found to be associated with previous microhaemorrhages on imaging, are lobar or superficial – particularly with rupture into the subarachnoid space, and not associated with any other demonstrable cause of ICH are likely to be related to CAA (111, 113-115). Apart from the presence of CAA itself, the most consistent

pathological association with ICH is fibrinoid necrosis affecting cortical arterioles (88, 97) but concentric splitting or cracking of the vessel wall, hyaline change and aneurysmal dilatation have also been reported (96, 116).

5.3. CAA increases the risk of cerebral infarction and ischaemic leucoencephalopathy

Patients with CAA have an increased risk of cerebral infarction (107, 112, 116-118). The infarcts tend to be cortical or in the subcortical white matter and to affect patients who have severe CAA with concentric splitting of the vessel wall (often associated with luminal stenosis), fibrinoid necrosis, acute vascular thrombosis or evidence of previous thrombosis and recanalisation.

Rarely, severe CAA causes a diffuse subcortical leucoencephalopathy. In some patients, this is associated with CAA-related inflammation or $A\beta$ -related angiitis (see below) but a leucoencephalopathy does occasionally develop in the absence of inflammatory vascular changes (119, 120). Impaired autoregulation of cerebral blood flow has been demonstrated in mouse models of CAA and is likely to be an important contributory factor in the development of CAA-associated leucoencephalopathy (121, 122).

There are conflicting data on the contribution of CAA to white matter abnormalities in AD. Haglund and Englund (123) found a correlation between the degree of white matter damage in AD and the ratio of $A\beta$ -laden to non- $A\beta$ -laden vessels in the frontal leptomeninges. However, others including ourselves did not find a significant relationship between CAA and white matter damage in AD (124-126). In our cohort, white matter gliosis (assessed by measuring the area fraction immunopositive for glial fibrillary acidic protein) correlated strongly with the parenchymal $A\beta$ and with axonal accumulation of APP but not with the severity of CAA (124).

5.3. In AD, CAA is associated with increased perivascular phospho-tau

In the most severe forms of CAA, many cerebrocortical arterioles show dyschoric amyloid angiopathy, in which $A\beta$ extends from the vessel wall into the adjacent parenchyma. This is often associated with accentuated perivascular neurofibrillary pathology (127-130), usually in the context of AD but sometimes even in its absence. It is of note that similar perivascular neurofibrillary pathology is also seen in severe amyloid angiopathy caused by vascular accumulation of amyloid peptides other than $A\beta$ – ABri and ADan in particular (2).

Although perivascular exacerbation of neurofibrillary pathology is most pronounced in association with dyschoric amyloid angiopathy, it is not restricted to this subset of patients. We performed a systematic analysis of the relationship of CAA to neurofibrillary pathology in sections of frontal, temporal and parietal cortex from cohorts of AD patients with moderate to severe CAA and with mild or absent CAA. Phospho-tau labelling of neurites around $A\beta$ -laden arteries and arterioles significantly

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exceeded that around non-A β -laden blood vessels and this, in turn was greater than the labelling of cortex away from blood vessels (131). The accumulation of phospho-tau around blood vessels with little or no amyloid suggests that the relationship is not simply a manifestation of a direct interaction between amyloid and adjacent neurites. It seems more likely that the CAA and the perivascular accumulation of phospho-tau are both consequences of elevated perivascular levels of soluble A β .

5.4. CAA may be associated with perivascular inflammation and angiitis

In some patients, the accumulation of A β in vessel walls induces inflammation. The severity varies and two main patterns of inflammation have been distinguished. The first consists of accumulation around A β -laden vessels of lymphocytes, macrophages and microglia, and occasionally multinucleated giant cells, but without actual vasculitis (132, 133). Eng *et al* (132) described the clinical and pathological findings in 7 such patients (from a consecutive series of 42 cases of CAA). The patients all presented with subacute cognitive decline or seizures, most had white matter abnormalities on neuroimaging and 5 were homozygous for *APOE* ϵ 4. Most improved clinically and radiologically after immunosuppressive treatment.

In some patients the inflammatory response leads to infiltration and necrosis of the walls of A β -laden blood vessels, a condition that we have called A β -related angiitis (ABRA) (46). The inflammatory infiltrate typically includes epithelioid and multinucleated macrophages (46, 134, 135) and is often associated with fibrinoid vascular necrosis, thrombosis or haemorrhage. Mononuclear inflammatory cells may also be more widely distributed within the leptomeninges. In our series (46), alterations in mental status (59%), headaches (35%), seizures and focal neurological deficits (24%) were common presenting features. Hallucinations were a presenting manifestation in 12% of cases. As in CAA-associated inflammation in the absence of angiitis (132), most patients with ABRA have white matter hyperintensities on MR imaging.

In ABRA, the cerebral cortex usually includes numerous activated microglia, occasionally in a plaque-like distribution and containing cytoplasmic A β (46). However, extracellular A β tends to be relatively sparse. This suggests that the vasculitis is part of a more widespread immune reaction to A β within the CNS.

6. CONCLUSION

The pathogenesis and pathogenicity of CAA are influenced by a range of processes that determine the absolute and relative amounts of A β 40 and A β 42 within the brain, the balance between parenchymal and vascular degradation of A β , and metabolic and physical constraints on its clearance along blood vessels into the CSF and across blood vessels into the circulation. Recent studies have emphasised the importance of the cerebral vasculature in regulating A β levels within the brain. This concept has

implications for our understanding of the relationship between AD and CAA and to our approach to the prevention and treatment of these diseases.

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