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REVIEW

Genetics and molecular pathogenesis of sporadic and hereditary cerebral amyloid angiopathies

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Abstract In cerebral amyloid angiopathy (CAA), amyloid fibrils deposit in walls of arteries, arterioles and less frequently in veins and capillaries of the central nervous system, often resulting in secondary degenerative vascular changes. Although the amyloid-β peptide is by far the commonest amyloid subunit implicated in sporadic and rarely in hereditary forms of CAA, a number of other proteins may also be involved in rare familial diseases in which CAA is also a characteristic morphological feature. These latter proteins include the ABri and ADan subunits in familial British dementia and familial Danish dementia, respectively, which are also known under the umbrella term *BRI2* gene-related dementias, variant cystatin C in hereditary cerebral haemorrhage with amyloidosis of Icelandic-type, variant transthyretins in meningo-vascular amyloidosis, disease-associated prion protein (PrP^{Sc}) in hereditary prion disease with premature stop codon mutations and mutated gelsolin (AGel) in familial amyloidosis of Finnish type. In this review, the characteristic morphological features of the different CAAs is described and the implication of the biochemical, genetic and transgenic animal data for the pathogenesis of CAA is discussed.

Keywords Central nervous system · Cerebral amyloid angiopathy · Amyloid proteins · Amyloid-β · ABri · ADan · Cystatin C · Transthyretin · Prion protein · Gelsolin · Genetics · Biochemistry · Pathogenesis

Introduction

Amyloid, which is ultrastructurally composed of highly insoluble, 8- to 10-nm wide fibrils, is the end product of a protein conformation disorder. The initial phase of amyloid formation is characterised by aggregation and polymerization of soluble, often circulating proteins, marked by the conversion of random-coil secondary structures into toxic β-sheet-rich conformations. Once such conformers have been produced and protein concentration has exceeded a critical level, protofibrillar intermediate species and subsequently high-ordered amyloid fibrils are formed [108]. A frequent precondition of amyloid formation is the proteolytic processing of a larger precursor protein. Examples of this include processing by the β- and γ-secretases of the amyloid precursor protein (APP), which releases the amyloid-β (Aβ) peptide in Alzheimer's disease (AD) [117] or processing by furin of the mutated BRI2 precursor proteins, which releases the ABri or ADan amyloid proteins in familial British dementia (FBD) [138] and familial Danish dementia (FDD) [140], respectively. A number of mechanisms are known to facilitate the destabilization of the

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secondary structure of soluble native proteins and these include genetic and posttranslational modifications, increased concentrations of proteins, low pH and the presence of metal ions, among others [108]. The genetic abnormalities include missense mutations in the coding region of a gene resulting in an amino acid substitution in an amyloid protein, which can alter or influence the rate of conversion of a native protein to a fibrillar conformer. A classical example is the mutant E22Q of the Aβ peptide, which is associated with hereditary cerebral haemorrhage with amyloidosis of Dutch type (HCHWA-D) [63]. Increased dosage of amyloid proteins is exemplified by trisomy of chromosome 21 in Down's syndrome or the duplication of the APP gene associated with early onset familial AD [83, 114]. A number of amyloid-associated proteins (AAPs) or 'pathological chaperons' co-deposit with different cerebral parenchymal and cerebrovascular amyloids. Such proteins are structurally and functionally diverse and their binding to the amyloid fibrils or their precursors may be additional factors influencing the formation of toxic misfolded proteins [34, 61].

The umbrella term cerebral amyloid angiopathy (CAA) describes a group of biochemically and genetically diverse disorders, which are unified by the morphological finding of amyloid fibrils deposited in the walls of small to medium-sized, mostly arterial blood vessels, and in some instances, also in capillaries of the CNS parenchyma and leptomeninges. CAA may contribute to cognitive decline due to cerebral ischaemia and microhaemorrhages [12, 41, 86, 93, 97, 121, 152]. As a result of degenerative changes secondary to amyloid deposition into blood vessel walls, they may become predisposed to rupture, which is a major cause of spontaneous, frequently recurrent, lobar cerebral haemorrhages in the elderly [91]. Data from animal models also suggest that CAA may exert a functional effect on cerebral microvasculature, leading to alterations in vessel tone and reactivity [58]. Inflammatory changes recognized as a significant clinicopathological feature of CAA could also play a potentially significant role in the pathogenesis of CAA-related ischaemia [115, 131, 144].

Out of more than 25 human proteins or their proteolytic fragments that have been identified to form amyloid fibrils in vivo, only 7 have been described in diseases of the central nervous system (CNS), in which CAA can also be a prominent feature [29, 108, 110]. The most common form of CAA is due to Aβ deposition, which occurs sporadically in the elderly or in association with AD. Aβ-CAA may also be prominent in variants of familial AD with mutations of the *APP,* presenilin-1 (*PSEN1*) or presenilin-2 (*PSEN2*) genes. CAAs associated with other amyloid proteins are rare hereditary conditions, which include (a) FBD with deposition of the amyloid protein ABri, (b) FDD with deposition of the amyloid subunit ADan, (c) hereditary cerebral haemorrhage with amyloidosis of Icelandic type (HCHW-I) with deposition of mutant cystatin C (ACys), (d) meningo-vascular amyloidosis with variant transthyretins (ATTR) as amyloid proteins, (e) variants of familial prion disease with vascular deposition of disease-associated prion protein (PrP^{Sc}), and (f) amyloidosis of Finnish type with mutated gelsolin (AGel) as its amyloid subunit.

In this review, we wish to discuss the major neuropathological, biochemical and genetic features of the different forms of CAAs and also their clinical significance.

Neuropathology of CAA

Leptomeningeal and cortical small and medium-sized arteries and arterioles are most frequently affected by amyloid deposition, although veins may also be involved. Blood vessels with advanced CAA show an acellular thickening with a smudgy appearance of their walls on the haematoxylin and eosin stained sections. Similar to amyloid deposits elsewhere, blood vessels with CAA appear apple green in Congo red preparations when viewed in polarized light, show green fluorescence when stained with Thioflavin S, and observed under ultraviolet light (Figs. 1, 2). Binding of both of these dyes is dependent on the high β-sheet content of amyloids and is considered specific in pathological practice [108]. The predilection sites of CAA due to Aβ deposition are the occipital, parietal, frontal and temporal lobes while the medial temporal structures and hippocampus are often spared [125]. Aβ-CAA has been reported to start in leptomeningeal or parenchymal blood vessels in the neocortex, followed by amyloid formation in blood vessels of allocortical regions and cerebellum and finally of deep grey nuclei, white matter and brainstem [124]. If capillary amyloid deposition is present, it can affect a number of areas, including neocortex, subiculum, CA1 and CA4 hippocampal subregions, amygdala, thalamus, hypothalamus, nucleus basalis of Meynert, midbrain, cerebellum and pons [126]. In some forms of familial CAAs including HCHWA-I, FBD and FDD, CAA is extensive and in addition to sites commonly affected by Aβ-CAA in most cases, it can also be found in cerebral and cerebellar white matter, deep grey nuclei, brainstem and spinal cord [47, 48, 99].

Cerebrovascular amyloid deposition is a multi-step process with Aβ first appearing around smooth muscle cells in the abluminal aspect of the tunica media and the adventitia [142]. This initial phase is followed by a gradual infiltration of the intimal layers by Aβ and with further progression amyloid will gradually replace the smooth muscle cells. A similar, gradual infiltration of blood vessel walls by ABri and ADan amyloid has also been documented by immunoelectron microscopic investigations [47, 48]. Degenerative changes may accompany the amyloid deposition, including

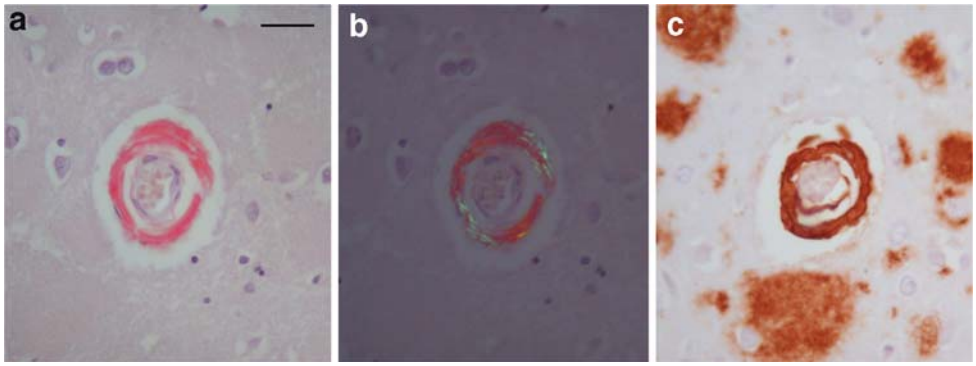

Fig. 1 **a** A Congo red-positive cortical arteriole in sporadic Aβ-CAA showing (**b**) characteristic apple green birefringence in polarised light. **c** Deposition of Aβ peptide in the vascular wall is extensive and double barrelling with 'vessel-within-vessel' appearance is also seen. The *bar* on **a** represents 30 μm on all images

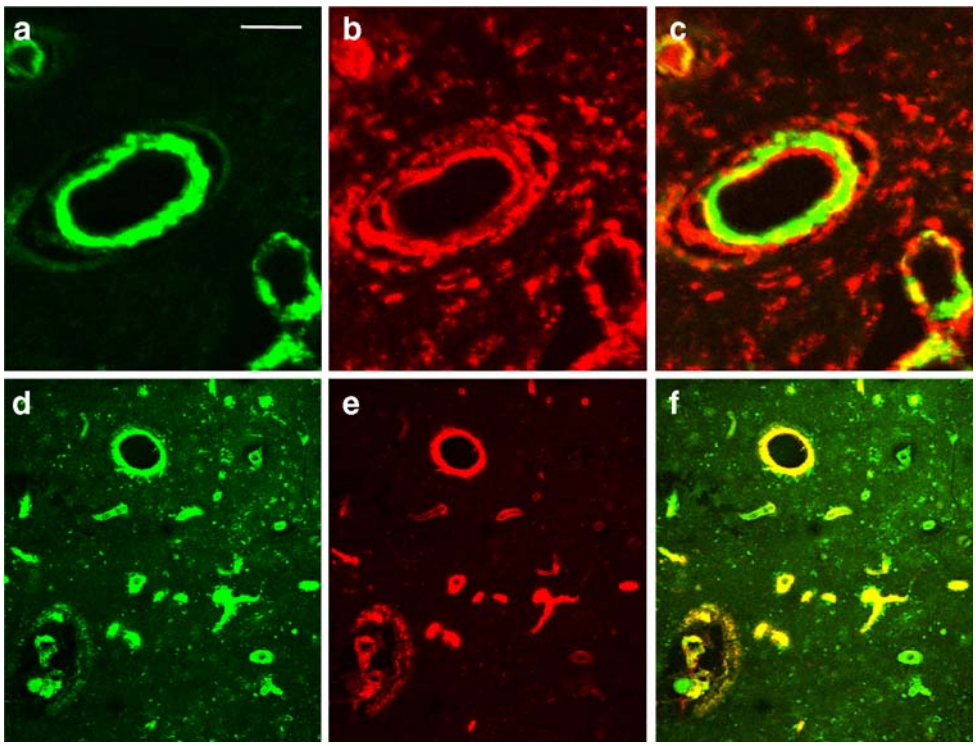

Fig. 2 **a**–**c** Marked activated microglial reaction in relation to amyloid laden blood vessels in familial British dementia (confocal microscopy, **a** Thioflavin S, **b** Cr3/43, **c** combined image). **d**–**f** The C1q component of the classical complement cascade co-localises with ADan deposition in cerebrovascular amyloid in familial Danish dementia (confocal microscopy, **a** ADan, **b** C1q, **c** combined image). The *bar* on **a** represents 30 μm on **a**–**c** and 60 μm on **d**–**f**

fibrous thickening with an "onion skin" appearance of the vessel wall, "double barrelling", thinning of the degenerative vessel wall sometimes with microaneurysm formation, fibrinoid necrosis and evidence of blood breakdown products around affected blood vessels [145]. CAA grading systems commonly used in research are taken into consideration in this process of progressive amyloid deposition [92, 146]. According to one of the frequently used systems in "mild" CAA, there is amyloid in the media without significant smooth muscle cell loss, while in "moderate" CAA together with the expansion of amyloid deposition in the media, smooth muscle cell loss is conspicuous. In "severe" CAA, the smooth muscle cell layer loss is complete and this is accompanied by degenerative changes of the affected vessel walls often with evidence of leakage of blood [146].

Irrespective of the nature of the amyloid protein, a significant perivascular inflammatory response with a prominent reaction by activated microglia and astrocytes and activation of the complement cascade around amyloid-laden vessels (Fig. 2) may be found in human and experimental CAAs [46–48, 112]. Such CAA-associated angiitis due to Aβ peptide deposition has now been defined as a clinicopathological entity with patients frequently presenting with alterations in mental status, headaches, seizures and focal neurological deficits [25, 115]. Pathologically Aβ-CAA related angiitis usually consists of angiodestructive inflammation with a pronounced adventitial and perivascular infiltrate of lymphocytes and histiocytes including multinucleate giant cells with Aβ phagocytosis as well as meningeal lymphocytosis [115, 156]. The likely trigger of the vasculitic process, which has also been documented in the APP23 transgenic mouse model of AD, is vascular Aβ-peptide deposition [3, 152, 156].

In brains with CAA-related haemorrhages, there may be several lobar haemorrhages showing different stages of organization. In some instances, microhaemorrhages can be

seen without evidence of a major lobar intracerebral haemorrhage. Loss of smooth muscle cells accompanied by degenerative changes, which results in weakening of the vessel walls, is thought to be the likely pathological substrate of the underlying blood vessel rupture. The possession of the ApoE ε2 allele has been reported to increase the risk of cerebral haemorrhage in patients with Aβ CAA and vasculopathic changes that result in blood vessel rupture [43, 88]. In transgenic animals with CAA, there is also a spatial and temporal relationship between microhaemorrhages and CAA. In addition, there is a positive correlation between haemorrhages and vascular amyloid load (for review see [45]). Cerebral infarctions and focal or diffuse white matter ischaemic lesions may also be the consequence of CAA irrespective of the nature of the vascular amyloid [39, 40, 66, 77, 100].

CAA with Aβ peptide deposition

Sporadic Aβ-CAA

The majority of Aβ-CAA is sporadic, mostly affecting elderly individuals, with or without morphological evidence of additional AD pathology (Fig. 1c). Sporadic CAA and AD have overlapping biology with shared risk factors [155]. The incidence of both diseases steadily increases with age with the incidence of CAA approaching 50% in elderly individuals aged over 70 years [8, 24, 27, 69, 75, 130, 143, 146]. CAA is present in over 80% of all AD cases [8, 24, 27, 69, 146] and involvement of capillaries by Aβ deposition is particularly overrepresented in advanced AD [4, 5].

Genetic risk factors for sporadic Aβ-CAA

The overlapping biology of CAA and AD is underpinned by the observation that CAA is more common and morphologically more severe in AD cases [155] than in controls and that genetic polymorphisms that have been described as risk factors for AD, such as those in ApoE, PS1, α-1-antichymotrypsin and neprilysin, which is one of the major Aβ degrading enzymes in the brain (see below), are also implicated in CAA [89]. The severity of CAA without significant AD pathology was found to correlate with the possession of the ApoE ε4 allele [105], which is also a risk factor for both sporadic CAA and CAA-related cerebral haemorrhage [42, 55, 105]. Increasing doses of ApoE ε4 have been shown to be associated with increasing amounts of $A\beta_{40}$ per affected cortical vessel without increasing the proportion of amyloid-laden vessels [2]. In AD, there is a strong association between the ε4 allele frequency and the severity of CAA [14, 53] and the occurrence of CAA-related cerebral haemorrhage [55, 105]. According to a more recent study, two types of sporadic CAA can be identified and the major difference between the two is the presence (CAA type 1) or absence (CAA type 2) of capillary amyloid. In CAA type 1 cases, the frequency of the ApoE ε4 allele is reported to be more common than in CAA type 2 cases and in controls [125]. Furthermore, individuals with AD and an ApoE ε4/ε4 genotype were found to have the overall greatest Aβ deposition, more frequent arteriolar Aβ deposition, in particular in white matter [132]. Although the mechanism underlying this increased risk is not entirely clear, there is evidence to show that ApoE binds to the low density lipoprotein receptor related protein-1 (LRP-1), and interacts with soluble and aggregated Aβ both in vitro and in vivo, influencing its conformation and clearance [49].

CAA in Alzheimer's disease treated with immunotherapy

Data are now available to indicate that following active immunisation of AD patients with Aβ42, in addition to a decrease in plaque load, there is probably a temporary manifold increase in the quantity of Aβ deposition in leptomeningeal and cerebral cortical blood vessels. This would be in keeping with observations made in immunised APP transgenic animals showing that plaque removal is accompanied by an increase in severity of CAA [102, 151]. Human studies have also demonstrated that CAA in patients treated with immunotherapy contains increased amounts of Aβ42 and Aβ40 due to solubilisation of parenchymal Aβ lesions and that, as in transgenic animals treated with passive immunisation, there is a higher density of microhaemorrhages and microvascular lesions [9, 98].

Hereditary CAAs due to Aβ peptide deposition

Missense mutations of the *APP* gene are within or just outside the coding region of the Aβ peptide (Fig. 3). Mutations, localized close to the β-secretase or γ-secretase cleavage sites with amino acid substitutions flanking the Aβ sequence, result in clinicopathological phenotypes of early onset AD, while those resulting in an amino acid substitution within residues 21–23 and 34 of the Aβ peptide are associated with a neuropathological phenotype, which also includes prominent CAA. The classical example of cerebrovascular disease manifestation is HCHWA-D, in which there is a glutamine for glutamic acid substitution at position 22 of Aβ (E22Q) due to a G for C nucleotide change at codon 693 of *APP* [63]. The clinical presentation of HCHWA-D includes strokes, including cerebral haemorrhage, although the initial presentation may be dementia [67]. Leptomeningeal and cerebral cortical blood vessels are affected by severe CAA (Fig. 4a) and, although diffuse Aβ plaques are found, classical dense core Aβ plaques are not seen and neurofibrillary degeneration is limited [67, 86].

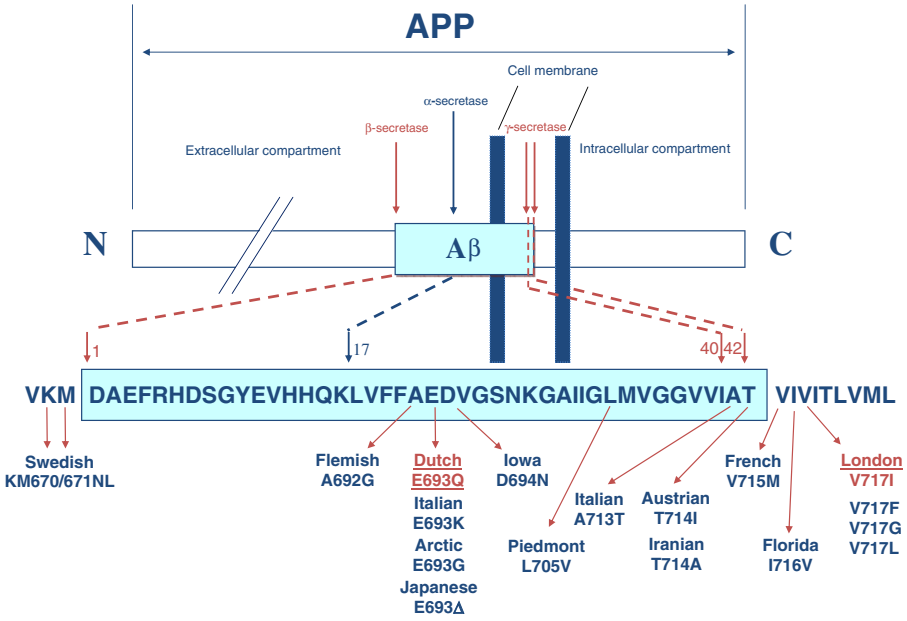

Fig. 3 Mutations in the APP gene and their relationship to the amino acid sequence of the Aβ peptide. The Dutch and London mutations of the *APP* gene, shown in *red*, were the first described within and outside the sequence of the Aβ peptide, respectively

In the Italian (E693 K), Arctic (E693G), Iowa (D694 N) and Piedmont (L705 V) variants, severe CAA has been confirmed to be a pathological feature, although it is not known why the Arctic and Iowa mutants co-exist with abundant neurofibrillary pathology while the Italian and Piedmont variants do not. The Flemish mutation (A692G) interferes with the normal processing APP and results in increased production of Aβ by the β-secretase homologue BACE-2. Affected individuals may develop cerebral haemorrhage or early onset AD. The neuropathological changes include neurofibrillary degeneration and AD-type Aβ parenchymal plaques, centered on blood vessels affected by CAA (for review see [158]). Recently, a novel mutation of the *APP* gene (E693Δ) was reported from Japan. This variant Aβ (E22Δ) lacking glutamate at position 22 is more resistant to proteolytic degradation and shows enhanced oligomerisation properties, but no fibrillisation. Although no neuropathological data have been reported to date, these data could be consistent with the hypothesis that the cause of dementia in this pedigree is due to enhanced formation of synaptotoxic Aβ oligomers [129]. Over-expression of wild-type APP without amino acid substitution in the protein sequence results in severe parenchymal and vascular Aβ deposition in early-onset familial AD caused by duplication of the APP gene and in Down syndrome [52, 114].

Severe Aβ CAA has been well documented in affected members of families with mutations in the *PSEN1* and *presenilin-2 PSEN2* genes [23, 50, 71, 90].

Aβ in blood vessels

Aβ deposited in blood vessel walls is highly heterogeneous at both N- and C-termini. Although Aβ species ending at position 40 are usually predominant, those ending at position 42 are often present and are particularly enriched in capillaries [5]. In some animal models, the first species deposited in the vessel wall is Aβ42 and the more soluble Aβ40 is deposited subsequently [133]. Aβ42 has been demonstrated in HCHWA-D cerebrovascular lesions [87] as well as co-deposited with ADan in FDD cases [48, 127]. N-terminally truncated and post-translationally modified Aβ species, which have enhanced aggregation propensities, have also been documented to contribute to vascular amyloid [123].

Biochemical studies of Aβ in HCHWA-D [104] and in the Iowa variant [128] of FAD demonstrated that the amyloid deposits in CAA are composed of both variant (either E22Q or D23N) and wild-type Aβ in ~50:50 ratio. Compared with wild-type Aβ, both the Dutch and Iowa Aβ40 synthetic peptides rapidly assemble to form amyloid fibrils in vitro, which are toxic to cultured human cerebrovascular endothelial cells and smooth muscle cells [79, 134]. In Aβ-CAA, a number of amyloid-associated proteins including complement components, serum amyloid-P component, Apolipoprotein E (ApoE), complement inhibitors such as apolipoprotein J (ApoJ) and vitronectin, α1-antichymotrypsin, glycosaminoglycans and extracellular matrix proteins are also present [136].

Clinical and experimental studies have demonstrated that in vivo the Aβ40:Aβ42 ratio is an important determinant of amyloid formation in different cerebral compartments, i.e. whether Aβ primarily deposits in blood vessel walls or brain parenchyma. There are considerable differences between these two major classes of Aβ protein species; Aβ42 aggregates more readily perhaps because it nucleates more efficiently. In contrast, the more soluble

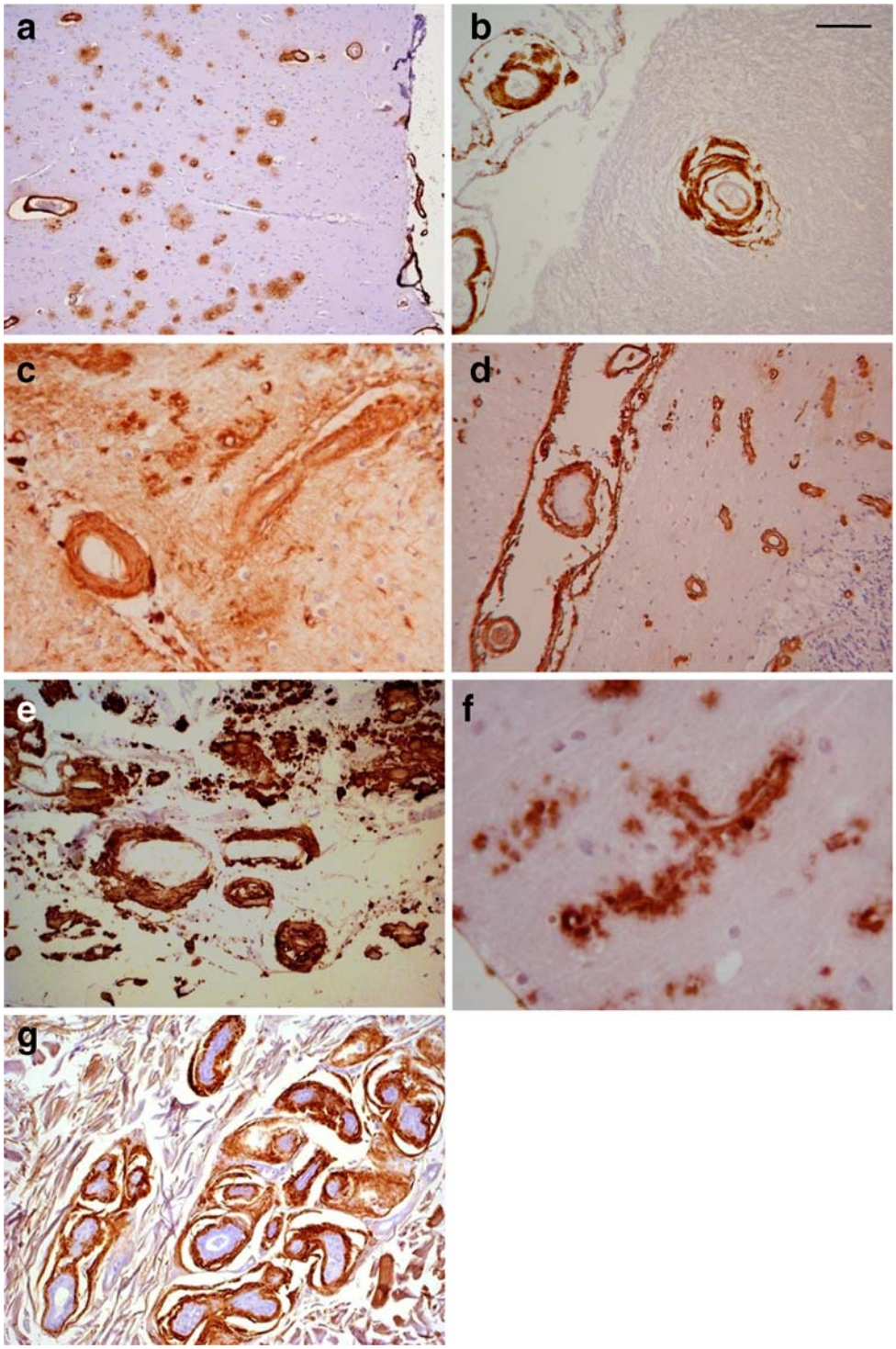

Fig. 4 Different amyloid peptides in hereditary CAAs. **a** Deposition of Aβ peptide in blood vessels and diffuse parenchymal plaques in cerebral cortex in HCHWA-D. **b** Accumulation of mutated cystatin C in leptomeningeal and cerebral cortical blood vessels in HCHWA-I. **c** Widespread deposition of ABri in FBD **d** and ADan in FDD is characteristic (**c** and **d**: cerebellar cortex). **e**: ATTR deposition is abundant in the leptomeninges and leptomeningeal blood vessels in the Hungarian form of meningovascular amyloidosis (lumbar cord). **f** PrP^{Sc} deposition in blood vessels and parenchyma is a characteristic morphological feature of human prion disease with the novel Y163STOP mutation of the *PRNP* gene (cerebellum). **g** Deposition of AGel in skin blood vessels in familial amyloidosis of the Finnish type. The *bar* on **b** repsents 60 μm on **a**, 30 μm on **b**–**e** and **g**, 15 μm on **f**

Aβ40 is less able to initiate nucleation events capable of promoting amyloid deposition, and it may also have a possible protective role with direct inhibitory effect on Aβ42 aggregation into amyloid both in vitro and in vivo [57, 76, 122]. The relationship between the Aβ40:Aβ42 ratio and the morphological phenotype is based on the different aggregation and fibrillisation propensities of the two major classes of Aβ when they are in different compositions [45]. An increase in total cerebral Aβ with an increase in both Aβ40 and Aβ42 levels, results in increased degree of amyloid deposition in both cerebral vasculature and parenchyma. An example is the KM670/671NL Swedish double mutation, which affects the two residues located just N-terminal to the β-secretase cleavage site and results in a

six to eightfold increase of both Aβ40 and Aβ42 [17, 84]. The neuropathological phenotype of both human disease and its transgenic animal model is characterised by a mixed plaque and CAA-rich picture [13, 60]. Overexpression of wild-type Aβ in familial AD with duplication of the *APP* gene and in Down syndrome has a similar effect with an increase of both Aβ40 and Aβ42 and amyloid deposition in both parenchyma and blood vessels [52, 114]. In contrast, mutations such as the London mutation (V717I), which are just C-terminal to the γ-secretase cleavage site of the *APP* gene, specifically increase the levels of the more insoluble and fibrillogenic Aβ42 and, as such mutations do not influence total Aβ production, there is a consequent decrease in the Aβ40 to Aβ42 ratio. In such human cases and their transgenic animal models there is significant parenchymal, but less vascular Aβ deposition [45]. In contrast, both human and experimental data indicate that an increased Aβ40 to Aβ42 ratio, such as that is found in affected members of families with HCHWA-D and the transgenic mouse model of this disease, significantly shifts Aβ deposition towards the cerebral vasculature resulting in prominent CAA [46]. That the high cerebral Aβ40 to Aβ42 ratio is an important marker of the morphological phenotype of HCHWA-D is further underpinned by data from experimental studies, in which the APPDutch mice were crossbred with mice overexpressing the hPS1 G384A mutation, which increases Aβ42 production. As a consequence, in the double-transgenic mice there is a decrease in the cerebral Aβ40 to Aβ42 ratio accompanied by a redistribution of the amyloid pathology from blood vessels to cerebral parenchyma [46].

Hereditary CAAs in FBD and FDD (*BRI2* gene-related dementias)

Two distinct mutations of the *BRI2* gene are associated with neurodegenerative diseases with striking morphological resemblance to AD. The neuropathological hallmarks of FBD include parenchymal ABri amyloid and preamyloid plaques, widespread ABri-CAA (Fig. 4c) and neurofibrillary tangle pathology [47, 100, 109, 153, 154]. In addition, white matter ischaemic change thought to be secondary to the severe CAA is also a characteristic feature [100]. The anatomical distribution of ADan deposition in FDD is rather similar to that seen in FBD (Fig. 4d), although the parenchymal lesions are primarily of preamyloid nature (defined ultrastructurally as granular, sparsely fibrillar protein deposits) [48]. In the Danish pedigree, there is also frequent co-deposition of Aβ, mostly Aβ42, with vascular and perivascular ADan amyloid [48, 127]. The *BRI2* gene is located on the long arm of chromosome 13 and is broadly expressed in a number of peripheral organs and neurons and glial cells of the CNS [62, 113, 138]. The *BRI2* gene encodes a 266-amino acid-long type II transmembrane protein, and furin-like proteolysis between peptide bonds 243 and 244 results in the release of a short 23-amino acid-long C-terminal peptide [138]. The BRI2 protein with a still largely unknown biological function, is widely expressed in the CNS and transported along axons [1, 62, 113]. BRI2 protein interacts with APP and is able to modify its processing. It may also act as a tumour suppressor and has been suggested to have pro-apoptotic properties [38].

A point mutation (T to A) of the normal stop codon of the *BRI2* gene is the genetic abnormality underlying FBD, while a 10-nt duplication insertion mutation between codons 265 and 266 is associated with FDD [38, 138, 140]. As both mutations abolish the normal stop codon, they result in extended precursor proteins, which possess 277 amino acids instead of the normal 266. In both diseases, 34-amino-acid-long C-terminal peptides, ABri in FBD and ADan in FDD, are cleaved from the mutated precursor proteins, and readily form amyloid fibrils in vitro. Both ABri and ADan are neurotoxic, which may partly be due to their ability to form ion channel-like structures in cell membranes [107]. ABri and ADan species with post-translationally modified N-termini, are the main components of the amyloid, preamyloid parenchymal deposits and vascular amyloid in the CNS and systemic organs in FBD and FDD, respectively [36, 127, 138, 140]. A constant feature of both FBD and FDD is that CAA is extensive and involves not only the blood vessels of the leptomeninges and cerebral cortex, but also of the white matter, deep grey nuclei, brainstem, cerebellum and spinal cord [47, 48, 100]. There is a wide range of amyloid-associated proteins in both ABri and ADan parenchymal lesions and CAA in a pattern similar to that seen in association with vascular and parenchymal Aβ deposits [61]. A marked astrocytic and activated microglial response together with complement activation of both the classical and alternative pathways have been documented in relation to ABri and ADan amyloid lesions, including CAA [47, 48, 62, 112]. As reported for other non-Aβ cerebral amyloidosis (see below), mostly vascular systemic deposits of ABri and ADan can be found in a variety of peripheral tissues [36].

CAA due to mutated cystatin C in hereditary cerebral haemorrhage with amyloidosis of Icelandic-type (HCHWA-I)

HCHWA-I is an autosomal dominant disorder with often fatal, early onset cerebral haemorrhage while dementia may develop in those surviving the initial episode of haemorrhagic stroke. HCHWA-I is associated with a glutamine for leucine amino acid substitution due to an A to T point

mutation at codon 68 of the *cystatin C* gene located on chromosome 20 [37, 64]. The cystatin C protein is a member of the type II family of cysteine protease inhibitors and is produced by many cell types including neurons of the CNS. The protein species widely deposited as vascular amyloid in the leptomeninges, cerebral cortex, basal ganglia, brainstem and cerebellum is an N-terminal degradation product of the mutated cystatin C protein. A characteristic feature of HCHWA-I is that in addition to CAA (Fig. 4b), as in FBD and FDD, amyloid deposits can also be found in peripheral tissues including lymphoid organs, skin, salivary glands, and testes [29].

CAAs due to deposition of variant transthyretins

Multiple mutations of the *TTR* gene, located on chromosome 18 are the most common cause of familial amyloid polyneuropathy. The amyloid subunit is composed of one of more than 60 known variants of the protein transthyretin, a molecule involved in the transport of the retinol and the thyroid hormone [51]. Although the major component of these amyloid lesions is mutated transthyretin (ATTR), wild-type transthyretin species have been also found incorporated in the amyloid fibrils [65, 103, 157]. As in other cerebral amyloidosis, amyloid fibrils are often composed of both full-length TTR as well as C- and N-terminal degradation fragments of various sizes.

The clinical manifestations of the disease are rather protean; phenotypic heterogeneity was not only found between mutations but among patients with the same mutation [18]. The most common neurological phenotype is familial amyloid sensorimotor polyneuropathy with or without associated autonomic neuropathy [7]. In some of the variants deposition of ATTR in the vitreous, leptomeninges and meningeal blood vessels is a feature. In the Hungarian (D18G) (Fig. 4e) and Ohio (V30G) pedigrees there is severe amyloid deposition in the leptomeninges and cerebral parenchyma and CAA is also documented [96, 139].

CAA in human prion diseases

A central feature of prion diseases is that disease-associated prions recruit normal cellular prion protein (PrP^{C}), encoded by a chromosomal gene (*PRPN)* localized on chromosome 20, and facilitate the conversion of the cellular isoform into a disease-associated prion protein isoform (PrP^{Sc}) [106]. PrP^{C} and PrP^{Sc} have an identical amino acid sequence, albeit with different conformations. While PrP^{C} is rich in α-helical regions, PrP^{Sc} is characterised by a β-pleated sheet-rich secondary structure. Limited proteolysis of PrP^{Sc} of about 142 amino acids length produces shorter, protease-resistant protein species (PrP 27-30), which is capable of polymerization and forming amyloid fibrils [106]. As a general rule, PrP^{Sc}-CAA is usually not a feature of human prion diseases, which include Creutzfeldt–Jakob disease (CJD), the Gerstmann–Sträussler–Scheinker's syndrome, fatal familial insomnia, kuru and variant CJD. However, rare hereditary disease forms, which are characterised by a premature stop codon mutation of the *PRPN* gene, seem to emerge as a noticeable exception to this general rule. Detailed neuropathological data are available from a family, in which a T to G mutation occurring at codon 145 results in an early stop codon (Y145STOP) and the production of an N- and C-terminally truncated, 70 amino acid-long PrP. In this pedigree, there is extensive PrP-positive CAA together with parenchymal perivascular PrP deposition and neurofibrillary tangle pathology [31]. One of us (JLH) recently had the opportunity to observe a case from a family with a novel Y163STOP mutation with a neuropathological phenotype characterised by vascular (Fig. 4f) and parenchymal disease-associated PrP deposition and extensive neurofibrillary tangle pathology (unpublished data). Both the Y145STOP and Y163STOP mutations result in truncated C-termini with loss of the glycosylphosphatidylinositol (GPI) anchor, which is added post-translationally to the C-terminus of PrP and is required to attach it to the outer leaflet of the plasma membrane [95]. As in the human disease due to Y145STOP or the Y163STOP mutation, in transgenic mice lacking the GPI anchor and infected with scrapie there are PrP^{Sc}-positive amyloid plaques and CAA. Data indicate that the GPI moiety might interfere with the ability of PrP to form amyloid fibrils and when it is absent, PrP readily forms amyloid fibrils also resulting in cerebrovascular amyloid deposition [15].

In a recently reported CJD case of an elderly individual, the accompanying CAA was mainly due to deposition of Aβ, although some additional PrP immunoreactivity was also observed [94]. It remains to be proven that this observation represents true vascular deposition of disease-associated PrP in a sporadic CJD case or the presence of PrP in the Aβ-CAA is more analogous to frequently observed co-deposition of PrP^{C} in Aβ amyloid plaques in AD [26].

Gelsolin-related-familial amyloidosis of the Finnish type

In this form of systemic amyloidosis, the clinical presentation includes ophthalmological, dermatological and neurological symptoms and signs. Both the G654A and the G654T mutations of the *gelsolin* gene located on chromosome 9 have been described in a number of countries, the G654A mutation is the characteristic genetic abnormality in the Finnish pedigrees. The actin-binding protein, gelsolin has two isoforms, one is cytoplasmic with a molecular

weight of 80 kDa while the other is present in the plasma and has a molecular weight of 83 kDa. The disease-associated variant AGel composing amyloid, consists of proteolytic fragments of the secretary form of gelsolin spanning positions 173–243 or 173–225 [35, 73]. Due to nucleotide changes noted above, AGel is characterised by a single amino acid substitution at residue 187, D187 N in the Finnish families and D187Y in the Danish/Czech kindreds [35, 73, 74]. AGel deposits in basement membranes and as amyloid angiopathy in systemic organs (Fig. 4g) and the CNS.

Pathogenesis of CAA

Studies of the mechanisms of disease pathogenesis in CAA are currently centered on the structural changes that affect the various amyloid subunits. Conformational transitions occurring in native soluble amyloid molecules increase their content in β-sheet structures favouring the formation of more insoluble oligomeric structures that are not physiologically catabolised and accumulate in the form of intra- and extra-cellular amorphous aggregates and fibrillar deposits. In turn, they trigger a secondary cascade of events that include, among others, release of inflammatory components, activation of the complement system, oxidative stress, alteration of the blood-brain barrier (BBB) permeability, formation of ion-like channels and cell toxicity [38, 111]. Although this information has been primarily obtained with the Aβ peptide it is clear that all known amyloid subunits share many aspects of these pathogenic mechanisms [111].

Aβ is a normal soluble component (sAβ) of biological fluids and brain interstitial fluid, in which its concentration appears to directly correlate with neuronal activity—being decreased under conditions of depressed neuronal function [10, 33, 85, 118, 120, 141]. Both deposited and sAβ molecules are identical in their primary structure, but exhibit completely different solubility and tinctorial properties. It is believed that the sAβ forms are immediate precursors of the deposited species, which through mechanisms, not completely understood, change their conformation into a predominantly β-sheet structure, highly prone to oligomerization and fibrillization. The identification of sAβ species in circulation, brain interstitial fluid and cerebrospinal fluid (CSF), together with the ability of the BBB to regulate Aβ transport in both directions, originally pointed out to the potential importance of plasma sAβ as the precursor of the deposited species [159]. However, the lack of brain lesions in a transgenic model with several fold increased plasma sAβ [56] strongly argues against the sole contribution of circulating species to brain deposition and draws attention to the brain itself as the source of Aβ. Since smooth muscle cells, pericytes and endothelial cells all express APP [11] and isolated cerebral microvessels and meningeal blood vessels are able to produce Aβ [54] the cerebral vasculature itself was proposed as a possible source of cerebral Aβ. This was supported by the close association of Aβ CAA with smooth-muscle cells [28]. Nevertheless, the sole contribution of smooth-muscle cells to Aβ-CAA is made less likely by the existence of amyloid deposits in capillaries (which are devoid of smooth muscle), a frequent finding in Aβ- as well as in ABri- and ADan- associated disorders [47, 48, 149]. Another argument against this hypothesis is that larger arteries with more abundant smooth muscle are usually less affected by amyloid deposition than small arteries and arterioles. In recent years, the notion of neuronal origin of Aβ and other amyloid proteins has been strengthened and is supported by the observation that APP transgenic models and more recently a transgenic model of FDD, all driven by neuronal promoters, develop CAA [11, 15, 46, 133, 137]. It has been proposed that the amyloid protein produced by neurons is drained along the perivascular interstitial fluid pathways of the brain parenchyma and leptomeninges and that under specific pathologic conditions it deposits along the vessels [149, 150].

With the exception of a small number (<5%) of AD familial cases with inherited mutations in *APP* or *PSEN* genes, no increased Aβ production has been demonstrated, suggesting an imbalance between Aβ production and clearance as a major element in the formation of amyloid deposits. The amphyphilic nature of Aβ precludes its crossing through the BBB unless mediated by specialised carriers and/or receptor transport mechanisms. In fact, the BBB has both the capability to control the uptake of circulating Aβ (free or complexed to carrier lipoproteins) into the CNS [20, 32, 68, 70, 72, 101, 160, 161] and regulate brain clearance via transport-mediated mechanisms [6, 21, 22, 30, 80, 119, 162]. Of the receptors involved, RAGE (the receptor for advance glycation end-products) actively participates in brain uptake of free Aβ at the vessel wall level [20] whereas other receptors are more relevant for the transport of Aβ complexed with other molecules, which, in turn, are ligands of specific receptors. In this sense, LRP-1 mediates transcytosis of Aβ-ApoE complexes contributing to rapid CNS clearance [119] whereas megalin mediates in the cellular uptake and transport of Aβ-ApoJ complexes across both the blood–brain and the blood–CSF barriers [161]. Also involved in Aβ efflux at the BBB is p-glycoprotein, highly expressed on the brain capillary endothelial cells, and the expression of which appears to correlate inversely with Aβ deposits [16, 59].

The notion of defective Aβ degradation as a contributing mechanism to brain accumulation should not be overlooked. Although the pathways by which Aβ is generated

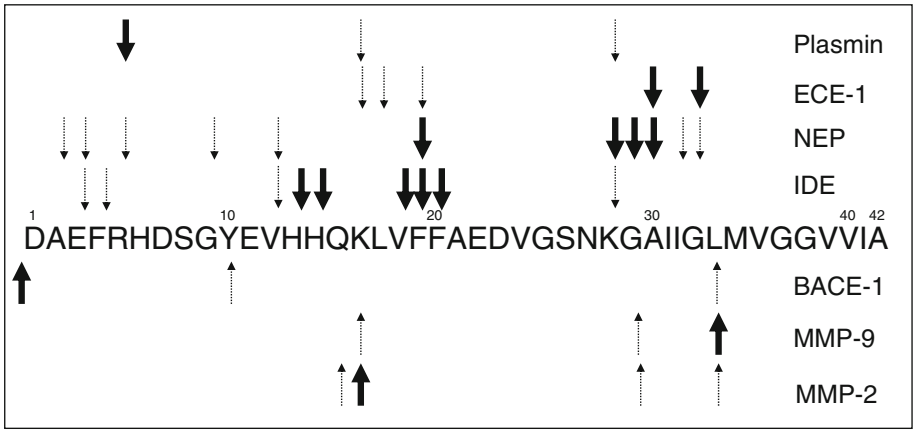

Fig. 5 Schematic representation of Aβ proteolysis by major Aβ-degrading enzymes. *Thick arrows* indicate major cleavage sites

from its precursor are largely known (Fig. 3), Aβ catabolism under physiological and pathological conditions is only starting to be unveiled. Neprilysin (NEP), endothelin-converting enzyme (ECE), insulin-degrading enzyme (IDE), beta-amyloid-converting enzyme 1 (BACE-1), plasmin and matrix metalloproteases (MMPs) are among the major enzymes known to participate in brain Aβ catabolic pathways (Fig. 5) (for review see [78, 81, 116, 148]). Reduced levels and/or catalytic activity of Aβ degrading enzymes as a result of age and genetic factors as well as specific disease conditions favour Aβ accumulation, an issue well documented in murine models in which gene deletion of different proteases translate into increased levels of Aβ deposition (for review see [116, 135, 148]). The specific association of many of these enzymes with vascular components points to their active participation in CAA pathogenesis [44, 82].

Experimental models of CAA

CAA due to deposition of Aβ has been reported in aged dogs and primates [147]. A number of transgenic mouse models with Aβ-CAA has been described, including the Tg2576 mice overexpressing human APP containing the Swedish double mutation under the control of a hamster PrP promoter. In the APP23 transgenic mouse model of AD, in which the same mutation is utilized under another neuron-specific promoter (murine Thy1), there is CAA with vasculopathic alterations and CAA-related cerebral haemorrhages, enhanced by either passive anti-Aβ immunotherapy or thrombolytic treatment [98, 152]. A significant degree of CAA has also been documented in aged mice with human APP transgene harbouring the London mutation. As already described above in detail there is severe CAA in the APPDutch mice, over-expressing E693Q-mutated human APP under the control of the neuron-specific murine Thy1 promoter [46]. In another transgenic mouse model (Tg-SwDI) expressing human APP possessing the Swedish double mutation and Dutch/Iowa (E693Q/D694 N) mutations at levels below those of endogenous mouse APP, the animals develop CAA in capillaries and occasional microhaemorrhages [19]. Recently an animal model of FDD has been described, which recapitulates major morphological features of the human disease including ADan parenchymal deposits and ADan-CAA [137].

Conclusions

The mechanisms of amyloid formation and deposition in cerebral blood vessels are certainly complex. Histopathological, biochemical, genetic and physicochemical studies in conjunction with data obtained from genetically engineered transgenic animal models support the notion that different amyloid subunits undergo common abnormal folding pathways rendering similar endpoint oligomeric and fibrillar structures that deposit in the vessels and eventually replace the whole vessel wall. Once established, these deposits alter the BBB permeability and affect the normal supply of oxygen and nutrients, triggering a cascade of secondary events that include inflammation, oxidative stress and cell toxicity, key elements in the development of neurodegeneration.

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