Cerebral Amyloid Angiopathies: A Pathologic, Biochemical, and Genetic View

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Abstract. Amyloid deposition can take place in the walls of arteries, arterioles, and, less often, capillaries and veins of the central nervous system, a phenomenon known as cerebral amyloid angiopathy (CAA). The major clinicopathological manifestations of CAA include cerebral hemorrhage, ischemic lesions, and dementia. CAA may be classified according to the amyloid protein deposited. In the most common form, sporadic CAA, and in CAA related to sporadic Alzheimer disease (AD), Aβ deposition is characteristic. CAA can also be severe in variants of familial AD caused by mutations of the amyloid-β precursor protein or presenilin-1 genes in which deposition of Aβ variants and/or wild-type Aβ occurs. Other amyloid proteins involved in familial CAA include 1) the mutant cystatin C (Cys) in hereditary cerebral hemorrhage with amyloidosis of Icelandic type, 2) variant transthyretins (ATVR) in meningo-vascular amyloidoses, 3) mutated gelsolin (AGel) in familial amyloidosis of Finnish type, 4) disease-associated prion protein (PrPsc) in a variant of the Gerstmann-Sträussler-Scheinker syndrome, and 5) ABri and ADan in CAAAs observed in the recently described BR2 gene-related dementia, familial British dementia and familial Danish dementia, respectively. This review addresses issues related to the correlation between morphology, biochemistry, and genetics, and briefly discusses both the pathogenesis and animal models of CAA.

Key Words: Amyloid proteins; Biochemistry; Cerebral amyloid angiopathy; Genetics; Hereditary cerebral amyloid angiopathies; Pathology.

INTRODUCTION AND HISTORY OF CEREBRAL AMYLOID ANGIOPATHY

Formation of amyloid is the end product of a protein misfolding disorder, during which proteins acquire a conformation rich in β-pleated sheet secondary structure, and through protofibrillar intermediates, form highly insoluble fibrils composed of protein polymers. Different amyloid deposits with similar ultrastructural features of 8- to 10-nm fibrils are composed of many different proteins with no obvious amino acid sequence homology. Of the more than 20 proteins or their proteolytic products that are now known to form amyloid fibrils in humans, around half a dozen proteins are implicated in diseases of the central nervous system (CNS) (Table) (1).

By destabilizing the structure of soluble native proteins, several factors are able to influence the process of fibril formation. The different likely mechanisms include genetic and post-translational modifications or increased concentrations of proteins, low pH and other unknown tissue factors, metal ions, and the deposition of a number of amyloid-associated proteins or chaperons (Fig. 1), which colocalize with the amyloid lesions, but are not part of the amyloid fibrils per se (2). Such amyloid-associated proteins include the serum amyloid-P component, apolipoprotein E (apoE), apolipoprotein J (apoJ), vitronectin, α1-antichymotrypsin, complement proteins, glycosaminoglycans, and extracellular matrix proteins. Genetic modification of precursor proteins, which after cleavage give rise to smaller amyloid proteins, is one of the best-studied factors influencing amyloid fibril formation. Of the genetic changes, amino acid substitutions due to point mutations in the coding region of a gene are the most common and these can alter or influence the rate of conversion of a native protein to fibrillar form. Examples of this include the amyloidogenic variant ACys, which deposits in hereditary cerebral hemorrhage with amyloidosis, Icelandic type (HCHWA-I), or the enhanced amyloidogenic properties of the mutant E22Q Aβ peptide that is associated with hereditary cerebral hemorrhage with amyloidosis—Dutch type (HCHWA-D). Truncation (Gerstmann-Sträussler-Scheinker with Y145STOP) and elongation (ABri and ADan precursor proteins in the BR2 gene-related dementia) of precursor proteins are further alternative mechanisms of genetic modification of precursor proteins resulting in amyloid formation.

The term cerebral amyloid angiopathy (CAA) is used to describe the pathological process during which an amyloid protein progressively deposits in blood vessel walls with subsequent degenerative vascular changes (3). In 1938, more than a decade after the first description by Divry of amyloid deposition in senile plaques in Alzheimer disease (AD), came the recognition by Scholz in Germany that amyloid can also be found in cerebral blood vessels in the brains of elderly patients. He also coined the frequently used term “druische Entartung,” often erroneously cited as “drusige Entartung,” to describe...
the phenomenon of amyloid spreading through the vessel wall into the surrounding neural parenchyma. In subsequent years, CAA was also observed as a feature of AD, including its atypical forms (for review see [4]). The earliest English language description of CAA was by Wors-ter-Drought et al in 1940 when they described a novel hereditary disease, which is now known as familial British dementia (FBD). However, without carrying out appropriate amyloid stains these latter authors initially did not recognize that the vascular changes were due to amyloid deposition and consequently they incorrectly described the vascular changes as “hyaline degeneration.” It was only several years later that the appropriate methods were employed and corrections in the literature could be made (4). The interest in CAA was significantly increased in the 1970s when it was recognized that CAA is often the cause of cerebral hemorrhage in elderly, non-hypertensive individuals (3). CAA was also described to be the salient or an important pathological feature of a number of familial conditions including HCHWA-I, familial AD including HCHWA-D, and in pedigrees with mutations of the TTR, GEL, or BRI2 genes (Table). The discovery of the biochemical and genetic abnormalities associated with these hereditary diseases and also that of Aβ peptide itself are good examples of the success of the research strategy, which was first used to identify the amyloid protein and later the genetic abnormality in HCHWA-I (for reviews see [1, 5]). This approach employs extraction of amyloid fibrils from leptomeningeal blood vessels to isolate amyloid proteins, which allows the identification of the sequence of a novel protein and subsequently the encoding gene and its mutation(s).

MORPHOLOGY

Light Microscopic Appearances

Amyloid deposition most frequently affects leptomeningeal and cortical small and medium-sized arteries and arterioles, which show an acellular thickening with a smudgy appearance of their walls on hematoxylin and eosin-stained sections (Fig. 2A), with a proportion of them also showing the characteristic appearances of “drusige Entartung.” As a general rule, veins and capillaries tend to be affected less frequently than arterial blood channels. Amyloid-laden blood vessels appear apple green when stained with Congo red and viewed in polarized light and show green fluorescence in Thioflavin S stains. Both preparations are considered specific, as they are dependent on the high β-sheet content of amyloid (Fig. 2B, C). Deposition of amyloid in blood vessel walls is a multi-step process. In the most extensively studied sporadic CAA it has been shown that amyloid initially tends to appear in the basement membrane around smooth muscle cells in the abluminal area of the media and adventitia (3). This is followed by progressive loss of smooth muscle cells and the appearance of vascular degenerative changes (6). The preservation of endothelial cells is usually a feature. For practical purposes, the grading system recommended by Vonsattel et al (7) for CAA can be useful. Amyloid is seen in the media without significant destruction of smooth muscle cells in “mild” CAA, while the smooth muscle cells are mainly absent in “moderate” CAA. Together with loss of smooth muscle cells, the presence of degenerative changes such as disruption of the architecture of affected blood vessels, double barreling, microaneurysm formation, fibrinoid necrosis, and leakage of blood through the blood vessel walls are seen in “severe” CAA. Demonstration of loss of smooth muscle cells may be a helper in determining the different morphological stages of CAA (Fig. 2 D–F).

Ultrastructural Appearances

Ultrastructural examination of arteries, arterioles, and capillaries in the leptomeninges and neocortex in cases
Fig. 1. Genetic and biochemical factors influencing conversion of native proteins into insoluble amyloid fibrils.

Fig. 2. Cerebral blood vessels with mural amyloid deposition (A) and double barreling (B, C) in a case of sporadic CAA with multiple cerebral hemorrhages (Fig. 4A, B) (A: Hematoxylin and eosin; B, C: Congo red). In the same case, increasing amyloid deposition is demonstrated to be associated with progressive smooth muscle cell loss (D–F) (arrow pointing to a preserved smooth muscle cell on F) (D–F: smooth muscle actin immunohistochemistry, SMA). Scale bar in panel A represents 20 μm in A, D–F; and 70 μm in B and C.

SPORADIC CAA

The majority of CAA is sporadic and is found in elderly individuals with or without morphological evidence of AD. CAA can be associated with cases of lobar cerebral hemorrhage, which accounts for approximately 12% to 15% of all cerebral hemorrhages in the elderly (5). Epidemiological studies, by demonstrating that the greatest attributable risk for this type of bleeding is the possession of either the apoE ε2 or ε4 allele (see also below), further support a link between CAA and such hemorrhages (10). In addition to cerebral hemorrhage (Fig. 4A, B), CAA can be associated with other neurological manifestations including transient neurological symptoms, CAA-associated vasculitis, presumably due to vascular Aβ, and it has also been suggested to be a cause of dementia (11). In support of this latter proposition are epidemiological studies showing that vascular factors, including CAA, play a role in the pathomechanism of dementia in AD (12). Although further clinicopathological studies are required to fully elucidate the pathogenic mechanisms by which CAA affects cognition, it seems...
Fig. 3. Immunoelectron microscopy demonstrating deposition of Aβ amyloid fibrils (arrow) in vessel walls. Early involvement of the basal lamina (b) in an arteriole showing preservation of the endothelium (e) (A). A vessel demonstrating advanced deposition of Aβ amyloid fibrils in the basal lamina (B). Scale bar in panel A represents 700 nm and 350 nm for panel B.

Fig. 4. Multiple cerebral hemorrhages of varying ages in a case with severe sporadic CAA (A, B). White matter atrophy and degeneration (C) and severe CAA (D) in a case of familial AD with PS1 E280G mutation (D: Aβ immunohistochemistry, scale bar represents 70 μm).
likely that ischemia and micro-hemorrhages related to CAA (Fig. 4C, D) play a significant part in this process (13–15). This is supported by clinicopathological studies demonstrating that the presence of extensive CAA alone is sufficient to cause dementia in some cases of HCHWA-D (15) and that CAA-related ischemia is also a determining morphological feature of the Iowa pedigree with the amyloid-b precursor protein (A\(\beta\)PP) D694N mutation (see also below) (16). Extensive CAA due to deposition of A\(\beta\)ri is also thought to be a contributing factor to dementia in FBD, in which diffuse white matter changes are a constant pathological finding (8). Although in these conditions with extensive CAA a unifying morphological feature is that of narrowing and occlusion of affected blood vessels (8, 15, 16), data from transgenic models of AD also suggest that CAA may have a significant effect on the physiology of cerebral microvasculature, resulting in alterations in vessel tone and reactivity even when amyloid deposition is mild (17). The presence of inflammatory components in association with CAA may have a potential role in promoting altered vessel function, which could be significant in the pathogenesis of CAA-related ischemia (18).

The overlapping biology of sporadic CAA and AD suggests that the 2 conditions share risk factors. The incidence of both diseases steadily increases with age and that of CAA may be as high as 46% in elderly individuals over 70 years of age (5). Compared with non-AD cases, the presence of AD further increases the frequency and severity of CAA pathology (19) and vascular amyloid deposition can be observed in more than 80% of all AD cases and is of moderate to severe degree in approximately one quarter (20). In this latter group of AD cases a higher incidence of cerebral hemorrhages and ischemic lesions can be observed (20). The apoE e4 allele has been identified as an important risk factor not only for sporadic and late-onset AD, but also for sporadic and AD-related CAA (21, 22). Increasing doses of apoE e4 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 (23). These latter observations have led to the hypothesis that apoE e4 enhances the accumulation of A\(\beta\)\(_{40}\) in blood vessels previously nucleated with A\(\beta\)\(_{42}\) rather than influencing the seeding process per se (23). In addition to apoE e4, the e2 allele has also been demonstrated to be associated with CAA-related cerebral hemorrhage by inducing amyloid-laden vessels to undergo vasculopathic changes leading to rupture (24). From all these observations it has been proposed that cerebral hemorrhage related to severe CAA consists of at least 3 distinct phases: 1) initial seeding of A\(\beta\)42, occurring in a subset of vessels or their segments; 2) expansion of the vascular amyloid deposits through the incorporation of A\(\beta\)\(_{40}\) to replace the vessel wall, a process that is enhanced by the possession of apoE e4; and 3) rupture of the vessel wall with hemorrhage, for which apoE e2 is a risk factor (23).

CAA IN FAMILIAL AD

The fact that AD is inherited in an autosomal dominant manner with almost complete penetrance in about 5% of cases makes familial AD epidemiologically the single most important hereditary condition that is associated with CAA. The missense mutations so far described in the A\(\beta\)PP gene, located on chromosome 21, are within or just outside the region encoding the A\(\beta\) peptide and localized near to one of the secretase cleavage sites (Fig. 5). According to their localizations, these mutations exert
their pathogenic effect through different mechanisms and often have characteristic clinical and pathological phenotypes. In general, substitutions affecting residues flanking the Aβ coding region of the AβPP gene give rise to early-onset AD, apparently through effects on the processing of AβPP (25). In the AβPP KM670/671NL Swedish double mutation, which affects the 2 residues located just before the N-terminus of Aβ, immediately preceding the β-secretase cleavage site, the pathological phenotype is that of AD with Aβ amyloid plaques as well as extensive neurofibrillary tangle pathology and CAA is not described as a prominent or consistent finding (26). This mutation induces increased cleavage by the β-secretases to generate more Aβ40 and Aβ42, although the Aβ species deposited in the brain is primarily Aβ42 (27).

Mutations occurring just C-terminal to the γ-secretase cleavage sites, including the “classical” London mutation (V717I), selectively enhance the production of Aβ species ending at residue 42 (25). In these mutants the morphological phenotype is identical with that seen in AD, including Aβ amyloid plaques and extensive neurofibrillary tangle pathology, although CAA is not a prominent feature. Mutations that result in an amino acid change within residues 21 and 23 of Aβ are associated with a clinical presentation that includes both hemorrhagic and ischemic strokes, and severe CAA is a pathological hallmark in these cases. G for C nucleotide change at codon 693 of AβPP resulting in a single amino acid substitution, glutamine for glutamic acid at position 22 of Aβ (E22Q), was the mutation first discovered in the AβPP gene, which is associated with the autosomal dominant condition HCHWA-D (28). In this disease, patients develop strokes, including cerebral hemorrhage and white matter changes (29). Some of the patients present with dementia in the absence of strokes and some develop dementia years after a stroke without additional such episodes. It has been suggested that severe CAA has a primary role in the dementing process in such individuals (15).

Neuropathologically severe deposition of Aβ affecting leptomeningeal arteries and cerebral cortical small arteries as well as arterioles (Fig. 6A), and to a lesser extent the cerebellar vessels, is characteristic (29). Parenchymal Aβ deposits of the diffuse plaque type are also present, but dense plaque cores are not seen and neurofibrillary degeneration is limited (15, 29). In the Italian (AβPP E693K) and Arctic (AβPP E693G) variants, vascular symptomatology has been described and severe CAA has been confirmed pathologically in both. Carriers of the AβPP A692G Flemish mutation are at risk for developing early-onset AD or cerebral hemorrhage and the pathological phenotype is unique in that it includes neurofibrillary degeneration and AD-type Aβ plaques with a large amyloid core, which have been shown to be centered on blood vessels affected by severe Aβ deposition (30). The AβPP D694N mutation has been described in an Iowa pedigree, in which the clinical phenotype is characterized by dementia and the pathological changes include leukoencephalopathy due to ischemia related to severe CAA. Neuropathological investigation shows numerous small cortical hemorrhages and both cortical as well as subcortical infarcts. Abundant neurofibrillary tangles and dystrophic neurites, which often occur around amyloid-laden blood vessels, are also present. Relatively sparse parenchymal plaques, generally of diffuse morphology and composed of Aβ40, have been described (16). Despite the close localization of these mutations with similarities in the clinical presentation, experimental studies have suggested that the Dutch and Iowa mutations exert their pathogenic effects through a mechanism that is strikingly different from that found in the Flemish mutation. Importantly, neither the Iowa nor the Dutch mutation seems to affect the amyloidogenic processing of AβPP, but has an effect on the aggregation and toxicity of these modified peptides (see also below). In contrast, the main effect of the Flemish mutation is that it interferes with the normal processing AβPP and leads to an increased production of Aβ by the β-secretase homologue BACE2 (31).

Severe CAA can also be associated with AD caused by mutations of the presenilin-1 (PS1) and presenilin-2 (PS2) genes. The pathological phenotype of several of the PS1 mutants includes severe CAA and a recent study has suggested that CAA is more severe in PS1 mutants in which mutations are located after codon 200 (32). In cases with Δ9 and ΔI83/ΔM84 mutations of the PS1 gene, the clinical phenotype can include spastic paraparesis (variant AD) and cotton wool plaques together with extensive and severe CAA (Fig. 6) (33). The predominance of cotton wool plaques is, however, not unique to these mutants as they have also been described in association with a number of other PS1 mutations. In these cases the clinical phenotype may or may not include spastic paraparesis (34). CAA has also been identified to be a prominent feature in a Volga-German family with familial AD due to the N141I mutation in the PS2 gene and cerebral hemorrhage was documented in at least one case (35).

Aβ species deposited in the blood vessel walls in sporadic AD and familial AD-related CAAs are pathogenic variants of a constitutive host protein, soluble Aβ (sAβ). Aβ and sAβ are 2 proteins with identical sequences that have different secondary structures responsible for their different physicochemical properties. These include the generation of β-sheet sheet conformations, resulting in aggregation and formation of insoluble amyloid fibrils (36). The Aβ species deposited in the blood vessel walls show both C and N-terminal heterogeneity that can be demonstrated with specific antibodies (Fig. 7A–F). Both
Fig. 6. Familial forms of CAAs. Deposition Aβ in parenchymal vessels and diffuse plaques in HCHWA-D (A) (Aβ immunohistochemistry). Severe CAA due to deposition ACys (inset) in HCHWA-I (B) (hematoxylin and eosin, inset ACys immunohistochemistry). Deposition of variant ATTR in blood vessel wall and leptomeninges in the Hungarian (D18G) form of meningo-vascular amyloidosis (C) (Hematoxylin and eosin; inset: TTR immunohistochemistry). Gelsolin deposition in skin blood vessels in familial amyloidosis—Finnish type (D) (Gelsolin immunohistochemistry). Extensive deposition of ABri in cerebellar blood vessels and parenchyma in familial British dementia (E, F). A parenchymal arteriole shows double barreling (F) and inset shows deposition of ABri in capillary wall (E, F; ABri immunohistochemistry). In familial Danish dementia deposition of ADan takes place mainly in blood vessels in the cerebellum (G). An affected vessel of the cerebellum showing an enhanced staining around the periphery (H). (G, H: ADan immunohistochemistry). Scale bar in panel A represents 70 μm in A, C, D, E, G and inset of B; 200 μm in panel B, inset in C; and 20 μm in panel F, inset in F and H.
immunohistochemical and biochemical studies have demonstrated that Aβ species ending at position 40 are predominantly deposited in the vessel walls in both sporadic and familial AD as well as HCHWA-D (37), and also that Aβ40 is not only present, but can sometimes be the sole deposited peptide species in CAA of both humans and transgenic animals (38). These observations, also supported by in vitro experiments (39), suggest that the first Aβ species deposited in the vessel wall end at position 42, while the more soluble Aβ40 is subsequently entrapped (38). An alternative possibility is that Aβ40 is produced in situ by degradation of Aβ42 by carboxy peptidases. The N-terminal heterogeneity of Aβ with a potential of such species for enhanced aggregation has also been documented in CAAs (40).

The biochemical and toxicological properties of the Aβ peptide species deposited in HCHWA-D and other variants caused by mutations of the AβPP gene have been extensively studied. In HCHWA-D, the amyloid deposited as CAA is composed of both variant (E22Q) and wild-type Aβ (41). Compared with wild-type Aβ, both the Dutch and Iowa Aβ40 synthetic peptides rapidly assemble to form fibrils in solution, while the Flemish Aβ40 peptide does not (42). Another feature of the Dutch and Iowa synthetic peptides is that they induce robust pathologic responses in cultured human cerebrovascular endothelial cells and are also toxic to smooth muscle cells (42, 43).

Similar to Aβ parenchymal lesions, Aβ in CAA is also associated with deposition of amyloid-associated proteins, including complement components, serum amyloid-P component, apoE, complement proteins, the complement inhibitors apoJ and vitronectin, α1-antichymotrypsin, glycosaminoglycans, and extracellular matrix proteins (44). Whether these unrelated proteins are key elements for the mechanism of fibril formation or are just innocent bystanders is, however, not known.

CEREBROVASCULAR DEPOSITION OF ACys IN HCHWA-I

HCHWA-I is an autosomal dominant condition of early onset. About half of the affected individuals clinically present with a fatal cerebral hemorrhage while they are in their twenties or thirties. In patients surviving the hemorrhagic episodes, cognitive decline and dementia may occur. Postmortem examination of brains of patients with HCHWA-I shows severe deposition of amyloid within small arteries and arterioles of leptomeninges, cerebral cortex, basal ganglia, brainstem, and cerebellum (Fig. 6B). In addition, asymptomatic amyloid deposits can be found in peripheral tissues, including skin, lymphoid tissues, salivary glands, and testes (1). The amyloid protein deposited in the CNS blood vessel walls is an N-terminal degradation product of cystatin C (Cyst C) bearing a single glutamine for leucine amino acid substitution due to an A for T point mutation at codon 68 of the cystatin C
gene \((\text{CYST} \ C)\), located on chromosome 20 \((45, 46)\). Cyst C is a low molecular weight member of the type II family of cysteine protease inhibitors and is produced by many cell types, including cortical neurons. Cyst C is normally present in biological fluids \((45)\), including in the cerebrospinal fluid (CSF). In patients with HCHWA-I, the CSF Cyst C levels were found to be half of those detected in healthy individuals \((47)\). The structural differences that exist between variant \((L68Q)\) and wild-type Cyst C account for the susceptibility of the variant protein to proteolysis and fibrillogenesis \((48)\). The possibility that Cyst C may have a role in the pathogenesis of other amyloidoses was raised by the observation that it is present in AD \((49)\), and that a polymorphism in the Cyst C gene may confer a greater risk of developing AD \((50)\). It is noteworthy that Cyst C is also present in the cerebral amyloid lesions in FBD \((51)\).

**MENINGO-VASCULAR AMYLOIDOSES RELATED TO ATTR DEPOSITION**

Amyloidoses due to mutations of the transthyretin \((\text{TTR})\) gene, located on chromosome 18, are late-onset autosomal dominant systemic diseases, in which deposition of one of the many variant transthyretin proteins \((\text{ATTR})\) takes place in multiple organs \((52)\). Functionally, transthyretin \((\text{TTR})\) is the main transporter of the retinol-binding protein in plasma and CSF and is the backup carrier protein for thyroid hormone. Wild-type TTR can be converted into intermediate conformers, followed by assembly into amyloid fibrils, which can deposit in the heart, resulting in cardiomyopathy in senile systemic amyloidosis \((53)\). Variant ATTRs are more amyloidogenic than the wild-type protein and more than 60 mutations of the TTR gene are now known to be associated with diseases \((52)\). In the formation of ATTR, dissociation of the normally folded tetrameric protein to a partially folded monomer that is capable of forming amyloid fibrils appears to be essential. It has also been suggested that single amino acid substitutions predispose TTR to fibril formation as they destabilize it by lowering the energy requirement for tetramer dissociation \((53)\). Patients with a familial disease have a considerably earlier onset of disease than in the sporadic form of transthyretin amyloidosis \((30 \text{ years versus} 80 \text{ years})\) and the most common neurological phenotype is familial amyloid (sensory) polyneuropathy, which can be coupled with autonomic neuropathy \((52)\). Systemic organs are commonly affected by ATTR deposition, which can also take place in the vitreous, leptomeninges, and meningeal vessels in some of the variants \((52)\). Involvement of the meninges and brain parenchyma is especially prominent in the Hungarian \((D18G)\) (Fig. 6C) and Ohio mutants \((V30G)\) \((54–56)\). In the former pedigree the clinical presentation includes memory disturbance, psychomotor retardation, ataxia, hearing loss, and, sometimes, spastic paraparesis. Involvement of systemic organs, peripheral nerves, and eye by amyloid deposition is not considered to be a feature \((54)\).

**CAA RELATED TO GELSOLIN AMYLOIDOSIS**

Gelsolin-related amyloidosis or familial amyloidosis, Finnish type \((\text{FAF})\) is an autosomal dominant condition characterized by systemic deposition of AGel. Although the majority of FAF patients have been reported from Finland, with a marked geographic clustering of cases in Southeastern Finland, the disease occurs worldwide \((57)\). The clinical presentation of FAF includes ophthalmologic, dermatologic, and neurologic symptoms and signs, although due to the systemic involvement, other clinical abnormalities may also occur \((57)\). In all the Finnish patients studied, a G654A mutation of the gelsolin gene \((\text{GEL})\), localized on chromosome 9, has been found \((57–59)\). The same mutation has also been reported from patients in other countries, although the G654T mutation is characteristic in the pedigrees reported from Denmark and Czechoslovakia \((57)\). Gelsolin is an actin-binding protein and is found as a cytoplasmic molecule \((80 \text{ kDa})\) and as a plasma isoform \((83 \text{ kDa})\), both encoded by the same \text{GEL} gene. AGel, deposited in tissues of FAF patients, consists of internal proteolytic fragments spanning positions 173-243 or 173-225 of the secretory form of gelsolin \((60)\). AGel contains a single amino acid substitution at residue 187, D187N in the Finnish kindreds, and D187Y in the Danish and Czech families \((61)\). The morphological findings are characterized by deposition of AGel in basement membranes and amyloid angiopathy (Fig. 6D) is also common in most of the organs, including the CNS \((57)\). In one of the Finnish pedigrees with G654A mutation, an extensive CAA in meningeal, cerebral, and spinal blood vessels has been found to be characteristic \((62)\).

**CAA RELATED TO PrP AMYLOIDOSIS**

In prion diseases the salient event is replication of the infectious prions by the process of recruiting normal cellular prion protein \((\text{PrP}^\text{C})\), encoded by a chromosomal gene \((\text{PRPN})\) localized on chromosome 20, and facilitating its conversion into the disease-associated (scrapie) prion protein isoform \((\text{PrP}^\text{Sc})\) \((63)\). Although \text{PrP}^\text{C} and \text{PrP}^\text{Sc} have the same amino acid sequence, they have different conformations: \text{PrP}^\text{C} is rich in \(\alpha\)-helicoidal regions while \text{PrP}^\text{Sc} contains stretches of \(\beta\)-pleated sheet secondary structure. Limited proteolysis of \text{PrP}^\text{Sc} results in a shorter, around 142 amino acid-long, protease-resistant molecule \((\text{PrP} 27-30)\), which is capable of polymerizing into amyloid fibrils \((63)\). In the human prion diseases, which include Creutzfeldt-Jakob disease, the Gerstmann-Sträussler-Scheinker syndrome \((\text{GSS})\), fatal familial insomnia, kuru and variant CJD, CAA due to deposition of
PrPSc is not characteristic and has been documented in only one pedigree with GSS (64). This GSS variant is caused by a T to G mutation occurring at codon 145 of the PRNP gene, which results in a premature stop codon (Y145STOP) and the production of an N- and C-terminally truncated PrP consisting of 70 amino acids (64). In this GSS variant the main neuropathological findings include PrP-immunoreactive CAA together with prominent perivascular PrP deposition and neurofibrillary tangle pathology (64).

CAA IN BRI2 GENE-RELATED DEMENTIAS

The 2 diseases so far described in this novel group of hereditary dementias in which severe CAA is one of the defining pathological hallmarks are FBD and FDD.

FBD is an autosomal dominant condition clinically characterized by progressive memory loss, spastic tetraparesis, and cerebellar ataxia with a disease onset in the sixth decade (65). Although CAA is extensive and severe in this condition, significant cerebral hemorrhage is relatively rare (65, 66). FDD was first described as heredopathia ophthalmo-oto-encephalica in a single Danish family (for review see [5]). Affected individuals of this family clinically first present in the third decade when they develop cataracts and ocular hemorrhages. Years later, hearing loss appears and patients subsequently develop cerebellar ataxia while they are in their forties, followed by psychiatric disturbances and dementia.

The genetic abnormality in both diseases results in elongation of the 266 amino-acid-long wild-type precursor protein, designated BRI-PP. The normal stop codon is replaced by arginine due to a T → A point mutation in FBD and is abolished by a frameshift caused by a 10-nucleotide duplication-insertion between codons 265 and 266, immediately before the stop codon in FDD (67, 68). Both mutations result in the same scenario of the production of 277 amino-acid-long mutated precursor proteins, designated as amyloid-Bri precursor protein in FBD and amyloid-Dan precursor protein in FDD. It has been shown that furin is able to process both the wild-type and mutated precursor proteins, resulting in the secretion of 23-amino-acid long wild-type and 34 amino-acid-long mutated C-terminal peptides (69). The amyloid peptides, designated as ABri in FBD and ADan in FDD, due to the nature of the mutations have unique 12-amino-acid-long C-terminal sequences that have allowed the generation of “mutation-specific” antibodies, recognizing exclusively either ABri or ADan.

Histologically, FBD is similar to AD in that the major pathological changes include severe, widespread CAA (Fig. 6E, F) and amyloid plaques, as well as neurofibrillary degeneration. The presence of ischemic white matter changes is also a feature in the majority of the cases. CAA affects small arteries and arterioles in the leptomeninges and both gray and white matter throughout the CNS with the exception of a few areas, such as the striatum (8). A proportion of the veins are also affected and involvement of some of the capillaries is also seen. As in Aβ-related CAA, degenerative changes of the amyloid-laden blood vessels, including double barreling or complete luminal obstruction, are present. The blood vessels of the retina show severe CAA (8), and blood vessels of systemic organs are also affected (70). All blood vessels affected by amyloid deposition stain positively with an antibody recognizing ABri (Fig. 6E, F). Argyrophilic, ABri-positive amyloid plaques of different sizes are most commonly found in limbic areas, while silver and Congo red-negative, ABri-positive “diffuse deposits” occur in several regions, including the entorhinal cortex and fusiform gyrus, where they are the main parenchymal lesion type (8). The neurofibrillary degeneration shows a close topographic association with both fibrillar and nonfibrillar ABri deposition.

Detailed neuropathological data are available in a few cases of FDD (9). The major histological features of FDD are similar to those seen in FBD and include widespread CAA (labeled with antibodies to ADan) and neurofibrillary degeneration (Fig. 6G, H). There are, however, differences in the neuropathological features between these 2 closely related diseases. In contrast to FBD, in which the extracellular ABri deposits form amyloid plaques, in FDD the predominant hippocampal parenchymal ADan deposits are Congo red and thioflavin S-negative, suggesting that ADan is in preamyloid (nonfibrillar) rather than amyloid (fibrillar) conformation in these lesions. In FDD the neurofibrillary pathology is severe in the limbic structures and is also present in neocortical areas where it is more severe than in FBD. Abnormal neurites, as in some other forms of CAAs, mainly cluster around CAA and are absent around nonfibrillar “diffuse” ADan parenchymal deposits. The retinal changes, with marked ADan amyloid angiopathy and parenchymal damage, are more severe in FDD than in FBD (9). A feature of the FDD cases, so far examined, is the deposition of variable amounts of Aβ peptide in blood vessels and brain parenchyma, which has been seen to occur either in isolation or in combination with deposition of ADan. The mechanism and significance of such a co-deposition of ADan and Aβ remains to be investigated.

Similar to sporadic CAA and AD, the vascular and parenchymal amyloid lesions in both FBD and FDD contain amyloid-associated proteins, including heparan sulfate proteoglycans, apoE, apoJ, vitronectin, and components of the classical and alternative complement pathways, suggesting in situ complement activation (5, 71).

MECHANISMS OF CAA

The origin of the different amyloid proteins deposited in cerebral blood vessels is poorly understood and a number of hypotheses have been proposed, which deal mainly
with the origin of Aβ in sporadic and AD-related CAs. As most cell types are able to produce AβPP, there are several theoretical possibilities for the origin of the Aβ deposits in cerebral blood vessels:

**Systemic Hypothesis:** Cerebrovascular Aβ deposits, similar to deposits in systemic amyloidoses, may derive from the circulation. In support of such a hypothesis is the observation that AβPP is expressed by almost all cell types in the body and is present in the plasma (72). Furthermore, the bi-directional receptor-mediated transport across the BBB and exchanges of Aβ between the CNS, blood, and CSF play an important role in determining Aβ concentration in the CNS, and a number of receptors, including the RAGE (receptor for advanced glycation end-products), LRP-1 (low-density lipoprotein receptor related protein-1), SR (scavenger receptor) and megalin receptors, have been implicated in this process (72). RAGE-mediated Aβ transport is present at the luminal side of the BBB, facilitating Aβ transport in a luminal to abluminal direction and allowing a significant influx of Aβ into the brain. In contrast, the LRP-1 receptor-mediated transport is initiated at the abluminal, CNS side and has a role in eliminating Aβ from the cerebral interstitial fluid. It is of note that one of the modulators of this process is the LRP-1 ligand apoE, which is also one of the risk factors of CAA (72). Another theoretical source of Aβ in CAA could be the CSF, where it is present in both normal individuals and AD patients (73, 74). The arguments against a blood-borne derivation of cerebrovascular Aβ include the finding that Aβ is first detectable morphologically in the abluminal basement membrane of blood vessels (75). Furthermore, transgenic mice over-expressing the 99-amino-acid C-terminal region of the human AβPP in multiple tissues, and showing exceptionally high levels of sAβ in the plasma, showed no changes in CNS up to the age 29 months (76). The more common involvement of arteries than veins and smaller arteries than larger ones in the subarachnoid space are arguments against a CSF origin of Aβ in CAA.

**Vascular Hypothesis:** The vascular hypothesis proposes that Aβ may derive from cerebrovascular cellular elements. This proposition is supported by the morphological observations showing that Aβ deposits are closely associated with cerebrovascular smooth muscle cells (77). It has been demonstrated that isolated cerebral microvessels and meningeal blood vessels are able to produce Aβ (78); smooth muscle cells, pericytes, and endothelial cells express AβPP, and degenerating smooth muscle cells and pericytes overproduce Aβ (for review see [79]). Arguments against the vascular hypothesis include the finding that Aβ deposits in capillaries and also that larger arteries, which have several layers of smooth muscle cells, are less affected than smaller ones (80).

**Drainage Hypothesis:** The drainage hypothesis proposes that Aβ, produced primarily by CNS neurons, is drained along the periarterial perivascular spaces of the brain parenchyma and leptomeninges, and CAA occurs due to deposition of Aβ along these drainage pathways (80). Degenerative vascular changes, which commonly affect aged individuals, could have a deleterious effect on the perivascular flow of interstitial fluid and be a factor in vascular deposition of Aβ. The presence of CAA in transgenic animal models of AD in which AβPP is expressed by neurons (see below) could also support the drainage hypothesis (38, 79).

Data suggest that some of the amyloid peptides implicated in familial CAs, such as ACys, ATTR, and AGel may derive from the circulation as they all also deposit in systemic organs. The origin of the amyloid peptides that are deposited in CAA and parenchymal plaques in FBD and FDD is not known. On the basis of the morphological similarities between these diseases and AD, one can postulate that ABri and ADan, as it has been suggested for Aβ in AD, could be produced by cellular elements of the CNS. In support of this proposition is the finding that BriPP mRNA (67) and protein (unpublished observations) are expressed in normal human brain. However, ABri is also found in the circulation and systemic deposition of ABri that takes place in FBD (70), which raises the possibility that peripherally produced ABri species could also be a source of CNS amyloid deposits.

**ANIMAL MODELS OF CAA**

The scarcity of animal models has delayed the experimental analysis of CAA. Previous studies were based on naturally occurring CAA due to deposition of Aβ in aged dogs and nonhuman primates. Although earlier transgenic animal models of AD had no, or subtle, involvement of the cerebral blood vessels by Aβ deposition, CAA has been reported in transgenic mice overexpressing human APP and co-expressing TGF-β1. In the APP23 mice in which a Thy-1 promoter is used to overexpress the Swedish mutant of APP, a significant degree of CAA was observed (79). A significant degree of CAA has also been described in aging APP/ld transgenic mice overexpressing the London mutant of human AβPP (38).

**CONCLUSIONS**

Sporadic CAA has been recognized as an important clinicopathological entity with an overlapping biology with AD. It is a major cause of cerebral hemorrhage in the elderly and data support a pathogenic role for CAA in dementia due to reduced blood flow. Although the familial forms of CAA are usually rare disorders, some of these, such as the BRI2 gene-related dementias, may provide an insight into the link between cerebral vascular and parenchymal amyloid deposition and neurodegeneration.
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