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Hereditary and sporadic beta-amyloidoses

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1. ABSTRACT

Cerebral amyloidoses are chronic, progressive neurodegenerative diseases that are caused by the aggregation and deposition of misfolded proteins in the central nervous system, and lead to cognitive deficits, stroke, and focal neurological dysfunction including cerebellar and extrapyramidal signs. Among them, beta-amyloidoses are a heterogenous set of conditions characterised by the deposition of beta-amyloid protein in brain parenchyma and/or vessel walls that lead to the development of two main clinico-pathological entities: Alzheimer's disease and cerebral amyloid angiopathy, which may be sporadic or familial, and may also co-exist in the same patient. The aim of this review is to describe the most important differences in the pathways leading to parenchymal and cerebrovascular beta-amyloidoses, and the main clinical, neuropathological and biochemical characteristics of the two conditions. It also discusses the phenotypes associated with a series of familial and sporadic beta-amyloidoses in more detail in order to highlight the clinical and neuropathological features that may help to distinguish the different forms of disease.

Table 1. Classification of cerebral amyloidoses

Amyloid protein	Disease
Beta-amyloid (Abeta)	1. Sporadic a. Sporadic Alzheimer's disease b. Sporadic cerebral amyloid angiopathy c. Amyloidosis associated with aging d. Amyloidosis associated with other conditions, including vasculitis, vascular malformations etc. 2. Hereditary a. Associated with mutations of the APP gene b. Associated with mutations of presenilin genes c Associated with Down syndrome
Cystatin C (A-Cys)	HCHWA-Icelandic type associated with a cystatin C gene mutation (Leu68Gln)
Prion protein (A-PrP)	PrP-CAA: Prion disease associated with a PRNP gene mutation (Y145stop)
A-Bri or A-WD A-Dan	Chromosome 13 dementias: British dementia (the Worster-Drought syndrome or familial British dementia) associated with a BRI2 gene point mutation at the stop codon Danish Dementia, associated with 10 nt duplication insertion mutation in the BRI2 gene
Transthyretin (ATTR)	Meningocerebrovascular involvement in familial TTR amyloidoses
Gelsolin (A-Gel)	Meningocerebrovascular involvement in gelsolin-related amyloidosis (familial amyloidosis, Finnish type)
Immunoglobulin light chain (AL-kappa, AL-lambda)	Amyloidoma Leptomeningeal vascular amyloidosis Solitary intracerebral plasmacytoma Primary intracerebral lymphoma with plasmacytic differentiation Multiple sclerosis with demyelination-associated amyloid deposition Widespread subcortical vascular amyloidosis with leukoencephalopathy (WSVAL)

2. INTRODUCTION

Amyloidosis is a protein conformation disorder that leads to the accumulation of insoluble protein deposits in various tissues, and causes organ dysfunction and cell death. The deposits mainly consist of self-assembled peptides that have a high content of beta-pleated sheet structure, the conformation responsible for their physico-chemical properties and tinctorial characteristics (1). "Amyloid" is a term applied to any proteinaceous tissue precipitate that binds Congo red dye (2), a property of all amyloids that does not depend on the type of amyloidogenic peptide and is only related to the propensity of the aggregates to form beta-sheet structures that subsequently assemble into fibrils (3).

Cerebral amyloidoses (Table 1) are part of a complex group of chronic and progressive neurodegenerative diseases characterised by protein misfolding and the intra- and/or extracellular accumulation of fibrillar aggregates (3). Of the more than 25 unrelated proteins known to produce amyloidosis in humans, only about one-third are associated with cerebral deposits that lead to cognitive deficits, dementia, stroke, cerebellar and extra-pyramidal signs, or various combinations of these (4).

Beta-amyloid-related amyloidosis (beta-amyloidosis) is here intended as the deposition in the central nervous system (CNS) of a 4 kDa amyloid beta (Abeta) peptide that derives from the larger amyloid precursor protein (APP) (5).

Abeta deposition in the CNS may involve the cerebral parenchyma and vessel walls, and leads to two main clinico-pathological entities: i) parenchymal amyloidosis and ii) vascular amyloidosis or cerebral amyloid angiopathy (CAA). These two conditions may co-exist (and often do) as they are caused by very similar pathogenic pathways.

Both parenchymal and vascular beta-amyloidoses characterise sporadic and familial Alzheimer's disease (AD), although their relative pathogenic contributions vary widely among different nosographic entities.

CAA is one of the major causes of cerebral hemorrhages, although it may also lead to ischemic lesions and dementia. Abeta-related CAA is a neuropathological hallmark that is not only associated with AD, but also with normal aging, Down syndrome, and sporadic cerebral amyloid angiopathy (sCAA) (3, 6).

Moreover, non-Abeta amyloid (mainly deposited in brain as CAA) is the main feature of a number of familial conditions, including transthyretin-related meningocerebrovascular amyloidosis of Hungarian and Ohio kindreds, gelsolin-related spinal and cerebral amyloid angiopathy, cystatin C-related amyloidosis, hereditary cerebral hemorrhage with amyloidosis of the Icelandic type (HCHWA-I), familial prion protein (PrP)-CAA, and Bri2-related familial dementia of British and Danish kindred (4,6,7,8), many of which involve the co- existence of parenchymal and vascular amyloid deposition.

3. ETIOPATHOGENESIS

The more than 25 different proteins that are known to self-assemble and form amyloid structures in humans are products of normal genes; however, a number of amyloid precursors contain abnormal amino acid substitutions that increase their potential for self-aggregation. The respective precursors are unrelated proteins that have a wide range of biological functions. Amyloid proteins share the conformational, immunogenic, and tinctorial properties described above, and typically consist of molecules whose mass is in the 4-30 kDa range with frequent heterogeneity at the amino and/or carboxyl-terminal ends (4). Increased levels of amyloid peptides may be due to the over-expression of their precursors (8) or an imbalance between production and clearance (4,7). There is evidence that the main cause of amyloid diseases lies in the intrinsic propensity of proteins to convert to the amyloid

state, and that the presence of sequence motifs encoding this type of structure may simply increase this propensity (9,10).

The most frequent forms of amyloidosis are those localised in the CNS and, among them, the Abeta-related amyloidoses due to deposition of Abeta peptides (8,11). There are different forms of Abeta, the most abundant of which is Abeta40 or Abeta1-40. Peptides with various amino termini but an identical carboxyl terminus account for more than 95% of the Abeta produced by cells under normal conditions, whereas less than 5% of newly generated Abeta ends at residue 42 (12). This "long Abeta" (also known as Abeta1-42 or Abeta42, and its N-terminal fragments AbetaX-42) aggregates more easily than Abeta40, is more represented in the insoluble fraction of brain tissue, and is believed to initiate the formation of oligomers, fibrils and amyloid deposition (13). The different Abeta peptides derive from the proteolysis of APP by the sequential processing of beta-site APP-cleaving enzyme 1 (BACE-1) or beta-secretase, and gamma-secretase, a protein complex with presenilin 1 at its catalytic core (14).

Cleavage by the alpha-secretase inside the Abeta sequence destroys the Abeta domain of APP and initiates so-called non-amyloidogenic APP processing, the prevalent pathway under physiological conditions. A large soluble amyloid precursor protein (sAPPalpha) ectodomain is released outside cells, and leaves behind an 83-residue carboxyl-terminal fragment (C83). C83 is digested by gamma-secretase to produce extracellular p3 and the amyloid intracellular domain (AICD), a short tail of approximately 50 amino acids that is released into the cytoplasm and targeted to the nucleus, where it is involved in activating signalling transcription. Conversely, amyloidogenic processing is initiated by beta-secretase and leads to the release of a shortened soluble APP fragment (sAPPbeta). The retained C99 is also a gamma-secretase substrate that generates Abeta and AICD (14-19).

The main factors inducing Abeta to accumulate in insoluble aggregates (which, according to the "amyloid cascade" hypothesis, are the most important players in the pathogenesis of AD) (20-22), are an imbalance between the production and clearance of Abeta peptides and/or their intrinsic propensity to aggregate. The aggregation process goes from the misfolded monomeric Abeta isoforms towards high-molecular-weight polymers through a long series of intermediates, each characterised by different structures and conformational properties. Different Abeta aggregates may form along the pathogenic chain but, as they are only transiently populated (23-25), the polymerisation pathway is a highly dynamic process. The isolation and characterisation of these aggregates are hampered by the use of solvent extraction procedures and detection methods (26,27) that make it difficult to differentiate their structural and neurotoxic features.

"Oligomeric" Abeta assemblies (dimers, trimers, etc.) are usually soluble in aqueous detergents, whereas protofibrils (PFs) are structures falling between oligomers and fibrils. The term "Abeta-derived diffusible ligands" (ADDLs) is also applied to pre-protofibrillar intermediates on the basis of their neurotoxic activity rather than their structural features (28), because it is believed that oligomers, PFs and ADDLs are the Abeta assembly states responsible for Abeta-induced neurotoxicity (29). The neurotoxicity of Abeta is not only due to its degree of oligomerization, but also to the specific structural conformation of the peptides in the assembly (30). The final assemblies, which are called fibrils because of their ultrastructural appearance, are the basic building blocks of amyloid plaque (Figure 1a).

However, there is no obvious correlation between the presence of Abeta-containing plaques in the brain and the severity of neurodegenerative symptoms in AD patients (31). A key question is the putative initial site of accumulation of Abeta species: a number of studies have reported the intraneuronal deposition of oligomerised Abeta42 (32,33), but whether this plays a significant role in human disease has not yet been firmly established. The accumulation of Abeta42 in the neurons of various transgenic animals seems to be better documented (34) but, as it could be caused by the over-expression of Abeta peptide in these animals, it can be extrapolated to familial AD but is not definitely applicable to sporadic AD (35).

Abeta oligomers induce localised increases of Ca2+ levels, the mis-sorting of tau in dendrites and tau hyperphosphorylation, thus triggering a parallel neurotoxic pathway that contributes to the pathogenesis of AD (36,37). Jin *et al.* (38) have recently isolated Abeta dimers (the most abundant form of soluble oligomers detectable in human brain) from the cortices of AD patients, and shown that they can induce the hyperphosphorylation of tau at AD-relevant epitopes and disrupt the microtubule cytoskeleton, thus causing neuritic degeneration. Moreover, Abeta amyloid peptides are capable of creating toxic membrane ion channels because of their capacity to self-assemble into annular structures (39). Soluble Abeta oligomers perturb metabolic processes, provoke the release of deleterious reactive compounds, reduce blood flow, induce mitochondrial apoptotic toxicity, and inhibit angiogenesis (22,40).

Together, these differentiated activities (most of which are intrinsic to Abeta aggregates and, according to recent data (39,41) retained by Abeta dimers) make up a powerful disease-promoting toxic machine.

The key pathogenic event in CAA is the deposition of amyloid on the walls of medium-sized and small leptomeningeal and cortical arteries, arterioles and, less frequently, capillaries and veins. How this occurs is a subject of debate (42). The various proposed mechanisms underlying the origin and production of Abeta in CAA include: 1) local production by smooth cells; 2) blood transfer; 3) brain parenchyma neuron involvement; and 4) vascular changes.

1) Smooth muscle cells (SMCs), pericytes and endothelial cells all express APP (43), and isolated cerebral

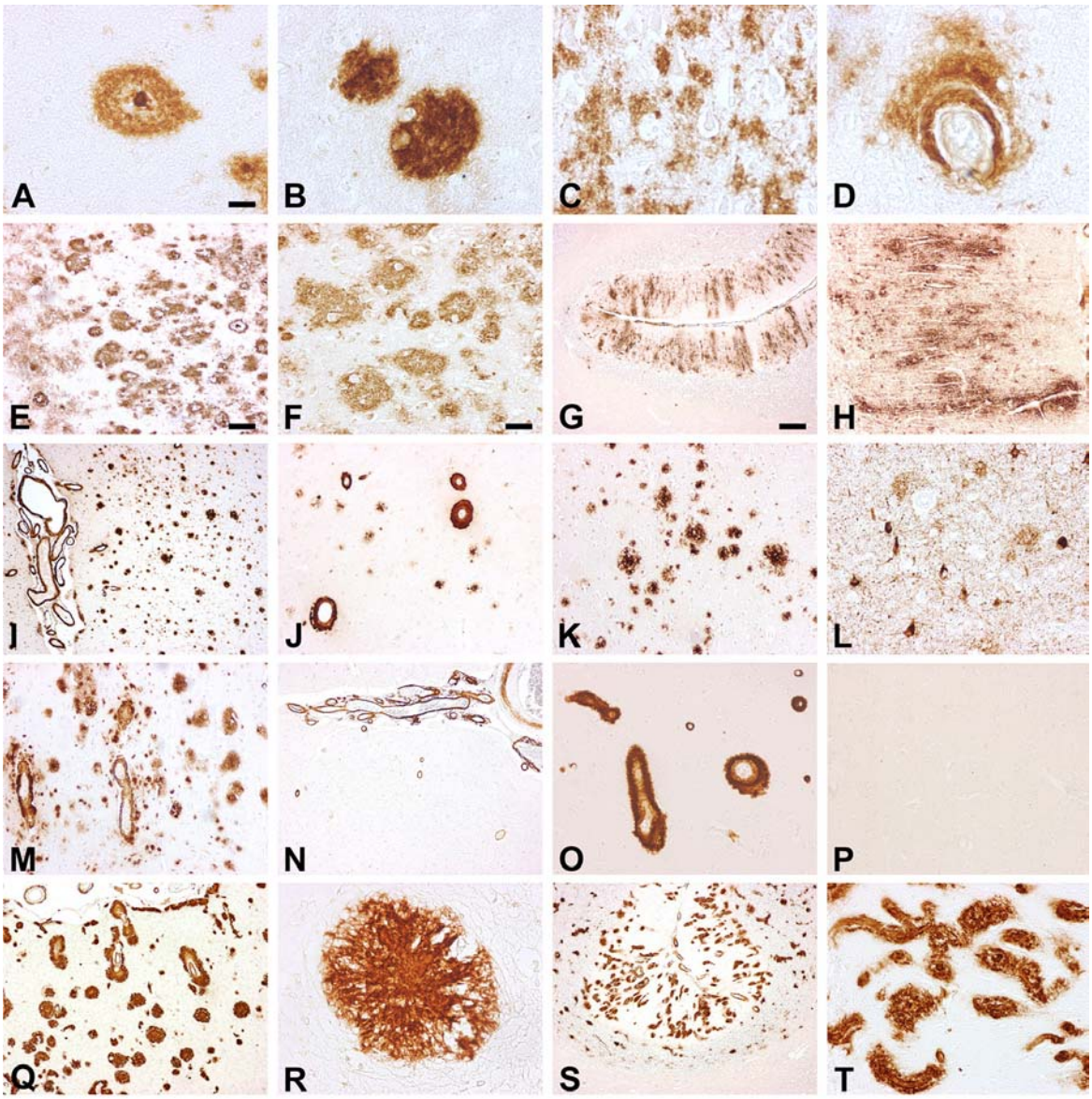

Figure 1. Neuropathological features of beta-amyloid amyloidoses. Paradigmatic illustrations of Abeta deposits in the neuropil and vessel walls of patients with sporadic AD (A-D), familial AD (E-H, PS1 P117A mutation), familial AD with severe amyloid angiopathy (I-L, APP A713T mutation), HCHWA with APP E693Q (M), APP L705V (N) and APP E693K mutations (O,P), and familial AD with a homozygous mutation (Q-T, APP A673V mutation). In the case of sporadic AD, there are different types of Abeta deposition: classic senile plaque with dense core (A), diffuse plaques (B), amorphous, finely granular pre-amyloid deposits (C), cerebral amyloid angiopathy (D). In familial AD with the PS1 P117A mutation, Abeta deposits are diffuse in most grey structures of the brain and are very abundant in the cerebral cortex (E,F) and cerebellum, with typical ribbon-like preamyloid deposits perpendicular to the pial surface (G,H). Familial AD with the APP A713T mutation is characterised by severe amyloid angiopathy (I,J). Senile plaques are also abundant (K), and co-exist with neurofibrillary changes revealed by immunostaining with anti-phosphorylated tau antibodies (L). The common features of HCHWA with the APP E693Q, APP L705V and APP E693K mutations are massive amyloid angiopathy in the leptomeningeal (N) and parenchymal vessels (O), associated with parenchymal deposits in the form of diffuse plaques in some cortical areas (M), in the absence of tau pathology (P). Familial AD with the homozygous APP A673V mutation is characterised by large, fringed plaques often adhering to the pial surface or the vessel walls (Q,R). The cerebellum is heavily involved, and the Abeta deposits are in the form of amyloid and associated with the vessels (S,T). Immunohistochemistry with antibodies against Abeta (4G8, A-K, M-O, Q-T) and phosphorylated tau (AT8, L and P) (immunoreactivity corresponds to a brown reaction product). Bar in A = 20 μm (A,B,C,D and R have the same magnification); bar in E = 80 μm (E,J,K,M,O and P have the same magnification); bar in F = 40 μm (F,H,L and T have the same magnification; bar in G = 200 μm (G,I,N and S have the same magnification).

microvessels and meningeal blood vessels are capable of producing Abeta (44); accordingly, the cerebral vasculature itself has been proposed as a possible source of cerebral Abeta. This hypothesis is supported by the close association between Abeta CAA and smooth muscle cells (45), but not by the existence of amyloid deposits in capillaries (which are devoid of smooth muscle) or the sporadic amyloid accumulation in arteries with more abundant smooth muscle cells than small arteries and arterioles (46).

2) The hypothesis that Abeta is transferred from blood to the cerebral vasculature is supported by the fact that Abeta may cross the blood/brain barrier (BBB) by binding to ApoE and ApoJ, or may itself induce BBB breakdown by impairing endothelial regulatory function and causing endothelial cell death (47-49). Moreover, Abeta has been detected in the cerebral vascular wall and parenchyma after its intravenous injection into rodents (50-52) and primates (53).

3) The observation that transgenic models showing the neuronal promoter-driven over-expression of APP develop CAA (7,54) has strengthened the idea of a neuronal origin of Abeta. It has been hypothesised that the Abeta produced by neurons is drained along the perivascular interstitial fluid of the brain parenchyma and leptomeninges and, under specific pathological conditions, deposited along the vessels (55,56).

4) Vascular changes may lead to Abeta deposition. This observation is supported by the detection of microvascular abnormalities in the brains of patients with pre-clinical AD before any evidence of neurodegenerative phenomena. Thickening and disruption of the capillary basement membrane could eventually induce Abeta deposition as various of its components (such as heparan sulphate proteoglycans, HSPGs) can facilitate Abeta deposition (57). Other microvascular changes, such as pericyte degeneration, endothelial cell shape changes and luminal buckling in brain capillaries may act by reducing cerebral blood flow (58).

Although Abeta is the primary component of senile plaques (SPs) and CAA, a number of observations suggest differences in their pathogenesis. The main differences relate to the composition of the amyloid deposits in terms of: a) Abeta content; b) the amount and type of non-Abeta peptides; and c) inflammatory changes.

a) The Abeta40 content of CAA is different from that of parenchymal deposits.

b) A number of molecules, such as heparan sulphate proteoglycans (HSPGs), are intimately associated with SPs and CAA. Various HSPG species have been characterised whose expression is different in the two conditions, including agrin, perlecan, syndecan and glypican (60), thus suggesting the specific involvement of HSPG species in the pathogenesis of CAA and SPs.

c) Inflammatory events are differentially involved in CAA and SP formation and development. The recruitment of inflammatory components in CAA is restricted to the activation of the complement system, and the main inflammatory proteins associated with SPs (i.e. alpha1-antichymotrypsin, alpha2-macroglobulin and intercellular adhesion molecule-1) are usually absent or only detectable in tiny amounts in CAA, which is characterised by the absence of activated cells of the monocyte/macrophage lineage around the CAA, thus suggesting an incomplete inflammatory response (42).

The epsilon4 allele of the ApoE gene is not only a risk factor for sporadic and late-onset familial AD (61), but also for sporadic and AD-related CAA (62). It has also been shown that inheritance of the ApoE epsilon2 allele is associated with CAA-related brain hemorrhages in AD and non-AD patients (63,64), although the underlying mechanisms are still unclear. ApoE deposition could be the first step in the disease process, followed by Abeta deposition in blood vessel walls and parenchyma. However, the most common finding is the co-localisation of ApoE and Abeta in amyloid lesions, and the amount of Abeta40 deposited in brain parenchyma and blood vessels closely correlates with the increased copy number of ApoE epsilon4 alleles. Other possible mechanisms underlying the more severe amyloidogenesis associated with the ApoE genotype include hypothesised critical interactions between ApoE and Abeta that may modulate the conformation and clearance of the latter (65).

4. NEUROPATHOLOGY

4.1. Abeta cerebral amyloid angiopathies (AbetaCAAs)

Cerebral amyloid angiopathy is mainly observed in the leptomeningeal and cortical small and medium-sized arteries and arterioles (Figure 1, panels D, I, J, N and O); veins are rarely also involved. The walls of blood vessels with advanced CAA are thickened and, like parenchymal amyloid deposits, they show birefringence in Congo red preparations when viewed in polarised light, and fluorescence when stained with Thioflavin S and viewed in ultraviolet light. The binding of both dyes is dependent on the high beta-sheet content of amyloid and considered specific in pathological practice (66). Amyloid angiopathy has been associated with fibrinoid necrosis and concentric splitting of blood vessel walls ("double-barrelled" appearance) (67). In the most severe cases, the walls of the small arteries and arterioles are replaced by amyloid deposits. Ultrastructurally, amyloid fibrils in blood vessels appear as interwoven bundles of 10 nm filaments that are rather short, arranged in a disorderly manner, and are first seen in the abluminal face of the basal lamina around smooth muscle cells, before gradually spreading towards the internal elastic lamina (67).

In addition to Abeta, other proteins such as apoE, cystatin C and the beta2-macroglobulin receptor/LDL receptor-related protein are also detectable (68-70).

The cerebrovascular Abeta deposits contain several forms of Abeta peptides and can be detected with antibodies against the different epitopes of Abeta. The Abeta40/Abeta42 ratio in CAA lesions is higher than in SPs (71), whereas the capillary Abeta deposits are attached

to the basement membrane (72) and their Abeta40/Abeta42 ratio is the same as that observed in SPs but significantly lower than that of affected arteries and veins (72,73). These data support the hypothesis that Abeta1-40 has a greater tendency to accumulate in the vessel wall, whereas Abeta1-42 is mainly deposited in SPs and CAA-affected capillaries (54,68).

Abeta-related CAA preferentially accumulates in the occipital, parietal, frontal and temporal lobes, and the medial temporal structures and hippocampus are often spared (74). It has been reported that Abeta CAA starts in the leptomeningeal or parenchymal blood vessels of the neocortex, and is followed by amyloid formation in the blood vessels of allocortical regions and the cerebellum, and finally of deep grey nuclei, white matter and the brainstem (75). Capillary involvement can sometimes be observed in the neocortex, amygdala, subiculum, hippocampus, thalamus, hypothalamus, brainstem and cerebellum (7). The amyloid deposits in capillaries (and occasionally arterioles or small arteries) infiltrate the surrounding parenchymal tissues, and are strictly associated with dystrophic neurites with which they form plaque-like structures (perivascular plaques or drüsige Entartung) (7). When CAA is extensive, it can also be found in the cerebral and cerebellar white matter, deep grey nuclei, brainstem and spinal cord (7, 76).

Cerebrovascular amyloid deposition is a multi-step process with medium-sized leptomeningeal arteries being affected in the outer portion of the media to the adventitia (77). This initial phase is followed by the gradual infiltration of the intimal layers by amyloid fibrils, which replace the smooth muscle cells and induce degenerative changes that include wall thickening/thinning, and “double barrelling”, sometimes with the formation of microaneurysms and fibrinoid necrosis, and the diffusion of blood breakdown products around affected vessels (78). CAA grading systems have been proposed by various authors: Vonsattel *et al.* classified CAA as “mild” in cases with evidence of amyloid deposition in the media without significant smooth muscle cell loss; “moderate” when amyloid deposition is extended to the media, and smooth muscle cell loss is more substantial; and “severe” when the loss of the smooth muscle cell layer is complete and associated with evidence of blood leakage (79).

Inflammatory reactions may be observed involving activated microglia and astrocytes, and activation of the complement cascade around amyloid-replaced vessels (80). These cases are characterised by the marked perivascular infiltration of lymphocytes and histiocytes, including multinucleate giant cells with Abeta phagocytosis (81), and are considered to be a distinct clinico-pathological entity that frequently presents with alterations in mental status, headache, seizures and focal neurological deficits (82).

As a consequence of this pathological restructuring of vessel architecture, the brains of affected patients usually undergo both microhemorrhagic and ischemic lesions. CAA has been found in 13% of tissue biopsies taken from subjects with a history of recent cerebral or cerebellar infarctions, but in only 3.7% of control specimens (83). Leukoencephalopathy may occur as a result of chronic hypoperfusion of the deep white matter, associated with CAA-related vascular changes of meningo-cortical segments of long perforating arteries/arterioles. It has been reported that the ApoE epsilon2 genotype increases the risk of cerebral hemorrhage in patients with Abeta CAA and structural changes that lead to blood vessel rupture (84). There is also a positive correlation between hemorrhaging and vascular amyloid load (85).

The different Abeta40/Abeta42 ratio between leptomeningeal and cortical amyloid deposits (71) induces speculation concerning the possible existence of different subtypes of sporadic CAA with distinct pathogenic mechanisms because capillary Abeta deposition is not always observed in CAA patients. However, cases with and without capillary CAA can be seen in every stage of CAA and AD. On this basis, some authors have suggested that the deposition of Abeta in capillaries reflects a distinct type of CAA (CAA type 1) which, unlike CAA type 2 (i.e. CAA lacking capillary involvement and segregation with the APOE epsilon4 genotype) is characterised by more frequent involvement of the white matter arterioles and associated with the APOE epsilon4 allele (86). Moreover, CAA type 1 is significantly associated with AD, especially advanced AD (65).

4.1.1. Sporadic and hereditary forms

The incidence and severity of sporadic forms of CAA increase with age (65,87). It is a common neuropathological finding in the brains of elderly individuals with or without evidence of AD (Figure 1, panel D). CAA has been found in 36% of subjects aged >60 years and 46% of those aged >70 years (87). In a study of 1981, the frequency of CAA varied from 8% (60-69 years) to 58% (>90 years) (88). The close association between CAA and AD has been shown by the fact that several studies have demonstrated the presence of CAA in more than 80% of AD cases (79,89). Moreover, a significantly higher proportion of hemorrhages (>5%) or ischemic lesions has been observed in cases with more substantial vascular amyloid deposition than in AD patients showing little or no amyloid angiopathy (90). In sporadic and AD-related CAA, amyloid deposition usually involves the occipital lobe more severely than other cortical areas (87). The most severe clinical consequence of CAA is cerebral hemorrhaging, which accounts for 12-15% of all cerebral hemorrhages in the elderly (90).

CAA is a common characteristic of familial pathological conditions caused by mutations in the APP, presenilin-1, or presenilin-2 genes (65). In these CAA-related conditions, whose prototypical disorder is the autosomal dominant condition known as hereditary cerebral hemorrhage with amyloidosis of the Dutch type (HCHWA-D) (91), cerebral hemorrhages or multiple strokes leading to vascular-type dementia (92) are very common, and associated with the severe deposition of beta-amyloid in leptomeningeal and cerebral cortical arteries and arterioles.

Diffuse parenchymal Abeta deposits are also present, but there is an absence of dense plaque cores and neurofibrillary tangles (93).

Other mutations within the Abeta region induce fully expressed AD with neurofibrillary changes, but are characterised by unusually severe CAA. Moreover, severe CAA can also be found in association with some presenilin-1 mutations (94,95), such as those occurring after codon 200, where extensive CAA is a distinguishing feature (96). Severe CAA also occurs in cases with Δ9 and DI83/DM84 mutations associated with variant AD with spastic paraparesis and cotton wool plaques (97). Finally, CAA is a prominent feature in the German family with AD due to the N141I mutation in the presenilin-2 gene (98).

4.2. Parenchymal Abeta amyloidoses [sporadic vs familial Alzheimer'a disease (AD)]

4.2.1. Sporadic AD

The neuropathological characteristic of AD is the co-occurrence of extracellular deposits of amyloid (Figure 1, panels A-D) consisting of ~10 nm straight fibrils whose main component is Abeta and the intra-neuronal build up of abnormally twisted (paired helical) filaments that are mainly composed of hyperphosphorylated tau protein. Abeta deposition takes place in the neuropil as well as in leptomeningeal and parenchymal vessel walls, whereas PHF formation occurs within the neuronal perykaria and neurites (99). Many AD patients also have co-existing pathologies such as Lewy bodies. A consensus panel from the United States and Europe has recently updated and revised the 1997 consensus guidelines for the neuropathological evaluation of AD, and these new guidelines recognise a pre-clinical stage of AD and establish protocols for the neuropathological assessment of the co-morbidities occurring in AD patients, such as Lewy body disease, vascular brain injury, hippocampal sclerosis, and TDP43-dependent pathology (100). However, tau, alpha-synuclein and TDP43 changes will not be considered in the current review.

One seminal question regarding the pathogenesis of AD is which of the two lesions (Abeta deposition or tau pathology) is more closely associated with the development of neuronal circuit degeneration and dysfunction, synaptic loss, and the appearance of cognitive deterioration. Further complexity comes from the observation that, albeit with differences in severity and topographic distribution, Abeta deposition and tau pathology may also be present in non-demented elderly subjects (101). However, in non-demented subjects, any neurofibrillary changes are usually confined to specific brain areas (the mesial temporal structures), whereas Abeta deposits may be abundant and diffuse in the neocortex, in some cases as abundant as in AD (99).

Abeta deposition in the neuropil leads to the formation of SPs (Figure 1, panel A), which are composite lesions whose morphogenesis is influenced by the participation of neuronal (neurites and synaptic terminals) or glial cellular elements (reactive astrocytes and activated microglia) (102).

The introduction of immunohistochemical techniques using antibodies against Abeta had a strong impact on studies aimed at elucidating the mechanism underlying SP formation. For example, it revealed a much denser and more widespread distribution of Abeta deposits in AD than had previously been found using of classic silver impregnation methods or amyloid-specific stainings such as Congo red or Thioflavin S. This was because Abeta immunostaining could also reveal Abeta deposits that lacked the tinctorial and ultrastructural properties of amyloid. These amorphous-looking and non-fibrillar plaques have been referred to as "pre-amyloid deposits" (Figure 1, panel C) as they might represent an early stage in the morphogenesis of SP, also bearing in mind that they are not associated with neuritic or glial changes (103). SPs lacking neuritic and glial components and showing a finely granular texture have also been called "diffuse plaques" (Figure 1, panel B), although this may give rise to confusion as it only describes the morphological appearance of the lesions and does not provide definite information as to whether they have the tinctorial and optical properties of amyloid fibrils.

It is widely accepted that these different types of Abeta deposits represent different steps in the formation of SPs. Some authors (104) consider the existence of four basic plaque types in a postulated maturation sequence: 1) early, amorphous, non-congophilic deposits of Abeta peptide without associated neuritic damage (diffuse, non-neuritic plaques; preamyloid deposits); 2) later deposits in which some granular condensation of Abeta has occurred, but without a congophilic core, and in which there is some evidence of neuritic damage (diffuse neuritic plaques); 3) a third step in which a central core of dense, congophilic amyloid is present (dense core, neuritic plaques); and 4) a late stage in which only the dense core persists, without diffuse amyloid or neuritic damage (dense core, non-neuritic plaques). These last plaques have also been called "compact", "end-stage" or "burnt-out" plaques. However, it is intriguing that, even at a late stage of disease progression, some regions of the brain such as the molecular layer of the cerebellum only contain pre-amyloid deposits.

Parenchymal Abeta deposits are associated with various proteins, lipids and cells: ApoE is an early and common component of the various types of deposit (99), but other molecules include cholesterol (105), ApoJ, tau protein, zinc, iron and copper ions, and various components of the extracellular matrix such as ICAM1, thrombospondin, heparan sulfate proteoglycan, as well as enzymes such as alpha1-antichymotrypsin (which may be involved in tau hyperphosphorylation), cystatin C and cathepsin D (99,106).

The brain topography of Abeta deposition depends on the stage of the disease. According to Braak's schema, it is possible to detect three stages of disease progression: stage A characterised by the presence of amyloid deposits in the ''basal portions'' of the cortex; stage B involving all of the isocortex except the primary cortices, and mildly affecting the hippocampus; and stage

C, which is associated with deposits in all areas of the isocortex including the sensory and motor cortices (107). Thal *et al.* proposed a refinement of this staging system and identified a sequence of involvement that begins with the neocortex and ends with the cerebellum (108).

Recently, Duyckaerts *et al.* (109) have proposed dividing the neuropathological changes of AD into three broad categories: lesions related to accumulation (''positive lesions''), alterations due to losses (''negative lesions''), and features due to reactive processes (inflammation and plasticity). The main features of negative lesions are neuronal loss, synaptic changes and spongiosis. It has been found that neuronal loss is focal in AD: severe neuronal loss has been documented in layer II of the entorhinal cortex (where it may reach 90% of the normal neuronal population in the most advanced cases), in the CA1 sector, in the superior temporal gyrus, and in the supramarginal gyrus (110). Synaptic pathology in AD can be summarised by two usual findings: a decrease in the total number of synapses as the disease progresses, and presence of degenerated synapses in SPs (110). The spongiform changes in AD vary, and may sometimes raise diagnostic difficulties with Creutzfeldt-Jakob disease (111).

Among the "reactive processes", the role of inflammation has been widely investigated over the last few years, and this has led to the identification of reactive astrocytes, activated microglia (112), early components of the complement cascade, and pro-inflammatory cytokines as proof of the mediation of inflammatory responses in the formation and maturation of SPs (113).

4.2.2. Familial AD

Cases of familial AD usually have a different pathological profile from that of the sporadic forms in terms of morphology, and the distribution and composition of parenchymal and vascular Abeta deposits. The association of parenchymal and vascular deposits is very frequent in cases of familial AD, particularly those related to mutations lying within the Abeta domain of the APP gene (see above), sometimes with peculiar features (114,115). More detailed clinico-pathological pictures of some specific inherited conditions will be described below.

5. CLINICAL PHENOTYPES

5.1. Clinical manifestations of Abeta CAAs

CAA may be associated with various clinical presentations including hemorrhagic or ischemic stroke; transient neurological syndromes such as TIAs, seizures and migraine; and cognitive impairment (116).

The most common clinical correlate of CAA is hemorrhagic stroke, which is frequently recurrent. Approximately 5-10% of lobar intracerebral hemorrhages (lobar ICH) in elderly subjects without hypertension are associated with CAA (the most common cause of intracerebral haemorrhage in the elderly) (117), whereas other causes such as vascular malformations predominate in younger patients. The clinical diagnosis of CAA is most often considered when an elderly patient presents with ICH in the cortical or cortico-subcortical regions of the brain, especially the frontal and parietal lobes; the cerebellum is much less frequently involved (118) and hematomas rarely extend towards the deep brain areas and ventricles. As lobar hemorrhages occur in subcortical regions under the pial surface, leaking of the hematoma into the subarachnoid space is common, but an isolated subarachnoid hemorrhage (SAH) without intraparenchymal blood is very rarely caused by CAA (116). Recurrent haemorrhages are a typical feature of CAA-related lobar hemorrhage in patients who survive the initial bleeding (119). A large ICH (5 mm) is most often acutely symptomatic and may manifest as headaches associated with emesis, focal neurological deficits, seizures, coma, or death (120).

The recurrence of lobar ICH is more common than that associated with hypertension (the estimated annual recurrence rate is 4.4-14.1%) (116), and a major cause of further morbidity.. The localisation of a CAA-related haemorrhage parallels CAA distribution in the cerebral cortex and cortico-subcortical or lobar regions (117). However, despite the high prevalence of CAA in the occipital cortex, CAA-related hemorrhages seem to be more evenly distributed, with a slight predominance in the occipital and frontal cortices (116,117).

Patients with Down's syndrome also experience strokes (121), and stroke-like events occur in 3% of AD patients with CAA; however, if cortical microhemorrhages are taken into account, the incidence of stroke-like phenomena in AD increases significantly (122). The CAA cases leading to stroke-like episodes are mainly those characterised by severely disrupted vessel walls, the formation of microaneurysms, and evidence of previous microscopic hemorrhages (117,123).

Over the age of 60 years, CAA is a rare cause of primary SAH, but the most frequent cause of ICH accompanying secondary SAH (124). In such cases, the subarachnoid hemorrhagic events are due to the extensive amyloid deposits in the meningo-cortical vessels.

The manifestations of cerebral ischemia should be included in the clinical spectrum of patients with hereditary or (less frequently) sporadic forms of CAA (116). The co-existence of a small cortical infarction and hemorrhaging is common (125). Ischemic events occur more often in the cerebral cortex, where they generate the so-called 'cortical lacunas' (125) that may present as TIAs or minor strokes in elderly CAA patients (127). CAA has been observed with ischemic infarctions, the transient neurological symptoms of which can include focal seizures, focal deficits, or positive visual symptoms similar to migrainous auras, which may sometimes precede major hemorrhagic events.

White matter ischemia due to CAA may lead to severe leukoencephalopathy (124,126). In the hereditary forms of Abeta CAA (e.g. Dutch and Iowa), the white matter damage is usually diffuse but, in sporadic Abeta CAA, it is often periventricular and characterised by gliosis, myelin loss, and hyalinisation of the blood vessel

Table 2. Diagnosis of CAA-related ICH - Boston criteria

Diagnosis	Criteria
Definite CAA	Full post-mortem examination demonstrating: lobar, cortical, or cortico-subcortical hemorrhage severe CAA with vasculopathy absence of any other diagnostic lesion
Probable CAA with supporting pathology	Clinical data and pathological tissue (evacuated hematoma or cortical biopsy) showing: lobar, cortical, or cortico-subcortical hemorrhage some degree of CAA in specimen absence of any other cause of hemorrhage, including: antecedent head trauma or ischemic stroke, central nervous system tumour, warfarin excess with INR >3, vascular malformation, or vasculitis.
	Clinical data and MRI or CT demonstrating: multiple hemorrhages restricted to lobar, cortical, or cortico- subcortical regions (cerebellar hemorrhage allowed) absence of any other cause of hemorrhage Age ≥55 years
Possible CAA	Clinical data and MRI or CT demonstrating: single lobar, cortical, or cortico-subcortical hemorrhage absence of any other cause of haemorrhage Age ≥55 years

walls (116). The main clinical manifestation of these changes may be progressive cognitive decline (123).

The neuro-imaging demonstration of a pattern of recent and older multiple lobar hemorrhages strongly supporta a clinical diagnosis of CAA. Magnetic resonance imaging (MRI) is the most useful, particularly gradient-echo sequences as they enhance the signal drop-out caused by iron products derived from subacute or chronic hemorrhages and allow the detection of even remote hemorrhages because the iron products are phagocyted by microglia and remain in the same location for a very long time (120).

Greenberg *et al.* (128) have shown that gradient-echo sequences are much more sensitive than conventional T2-weighted images, and very powerful in detecting the accumulation of new small asymptomatic hemorrhages over time as a marker of the progression of CAA and a prognostic index during follow-up. Patients showing more hemorrhages in their baseline scans are more likely to develop new hemorrhages as the disease progresses (129).

Leukoencephalopathy in CAA can be demonstrated by CT low attenuation of the white matter or high signal intensity of the white matter in T2-weighted MR images. It is a non-specific finding that may be due to demyelination, ischemia, infarction or edema, but CAA should be considered especially if the leukoencephalopathy is associated with cortical-subcortical hemorrhages or progressive dementia (130). Two imaging patterns of leukoencephalopathy in patients with CAA have been reported:

1) Leukoencephalopathy with the sparing of U fibres is characterised by the symmetrical periventricular distribution of white matter high signal intensity and atrophy, and is similar to the picture often observed in patients with Binswanger's subcortical encephalopathy;

2) Leukoencephalopathy with the involvement of U fibres is associated with a mass effect that is probably related to edema (130,131) and perivascular inflammation as a neuropathological correlate. T2-weighted MR images show white matter high signal intensity prevalently in the centrum semiovale and deep periventricular regions, sparing the corpus callosum and internal capsule.

The development of the Boston criteria (Table 2) for the diagnosis of CAA in 1995 and 1996 by Greenberg *et al.* (64,132) improved the clinical detection of disease and standardised the diagnosis of CAA-related ICH. These criteria use clinical, radiological and pathological data to classify lobar ICH as possibly, probably or definitely CAA-related (133). An age of more than 55 years is required for a clinical diagnosis because CAA is rare (but not unheard of) in younger patients. The ability to diagnose probable CAA in a patient presenting with a first ICH is greatly enhanced by the use of gradient-echo MRI to detect remote asymptomatic hemorrhages, which is highly recommended.

Hereditary forms of Abeta-related CAA (hbetaCAA) are rare and account for a minority of CAA cases. Their phenotypical variability is a relevant feature because the clinical characteristics within the hereditary group include a broader spectrum of presentations than those associated with sporadic disease, and usually have an earlier onset. The clinical signs of the hereditary forms can include spastic paraparesis, extrapyramidal signs, progressive ataxia or ocular disturbances, none of which are part of the spectrum of sporadic cases (116).

5.2. Clinical manifestations in Abeta-related parenchymal amyloidoses

5.2.1. Sporadic AD

Late-onset sporadic AD is the most common form of dementia in humans aged >65 years, and affects more than 50% aged >85 years. It is a debilitating neurodegenerative disorder that affects millions of people.

It is widely accepted that the clinical alterations in AD patients correlate with tau-related rather than amyloid-related pathology. As reviewed by Storey *et al.* (134), the temporal evolution of the topographic distribution of plaques and NFTs parallels the onset and progression of the neuropsychological deficits. The initial and typical involvement of mesial temporal structures (107) leads to the early impairment of anterograde episodic memory, and the cognitive domain to be involved is usually semantic memory, which correlates with the spread of NFT's to the lateral temporal neocortex. Selective attention may also be disturbed at this stage (135). In the middle stages of the disease, its spread to the temporoparietal association cortex may manifest itself as impaired comprehension, visuo-perceptual dysfunction and apraxia. The prefrontal association cortex may also be affected, thus impairing sequencing, planning and self-monitoring. The primary motor, sensory and (usually) visual cortices are relatively spared, correlating with a paucity of motor, somatic sensory and visual findings upon neurological

Table 3. AD diagnostic criteria

Diagnosis	Criteria
Definite AD	Presence of clinical and histopathological evidence of disease (brain biopsy or autopsy), as required by the NIA-Reagan criteria for the post-mortem diagnosis of AD; or Presence of clinical and genetic evidence of AD (APP or PS1 or PS2 gene mutations).
Probable AD: core diagnostic criteria (A) plus one or more supportive features (B, C, D, or E)	Core diagnostic criteria A. Presence of early and significant episodic memory impairment that includes the following features: Gradual and progressive change in memory function reported by patients or informants over more than 6 months; Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly or does not normalise with cueing or recognition testing and after effective encoding of information has been previously controlled; The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances.
	Supportive features B. Presence of medial temporal lobe atrophy Volume loss of hippocampi, entorhinal cortex, amygdala revealed by MRI with qualitative ratings using visual scoring (referenced to a well-characterised population with age norms) or quantitative volumetry of regions of interest (referenced to a well-characterised population with age norms); C. Abnormal cerebrospinal fluid biomarker Low amyloid β1-42 concentration, increased total tau concentration, or increased phospho-tau concentration, or combinations of the three; Other well-validated markers to be discovered in the future; D. Specific pattern on PET functional neuroimaging Reduced glucose metabolism in bilateral temporal parietal regions Other well-validated ligands, including Pittsburg compound B or FDDNP or others; E. Proven AD autosomal dominant mutation within the immediate family.
	Exclusion criteria History Sudden onset Early occurrence of the following symptoms: gait disturbances, seizures, behavioural changes Clinical features Focal neurological features including hemiparesis, sensory loss, visual field deficits Early extrapyramidal signs Other medical disorders severe enough to account for memory and related symptoms Non-AD dementia Major depression Cerebrovascular disease Toxic and metabolic abnormalities, all of which may require specific investigations MRI FLAIR or T2 signal abnormalities in the medial temporal lobe consistent with infectious or vascular insults.

examination. In the later stages of the disease, patients are unable to cooperate meaningfully with standard neuropsychological assessments, although specialised cognitive batteries may still delineate residual capabilities (136). From the above, it is clear that tests of anterograde episodic memory should be the most sensitive to early AD, and the same memory might be expected to be the first cognitive domain affected in the case of incipient AD. Most clinical studies of incipient AD have confirmed this expectation but, as the clinical presentation may be substantially different from the paradigm described above, it is likely that there are several variants of sporadic AD that have not yet been extensively characterised (134).

Neuropsychological impairment cannot be detected before significant neuronal dysfunction has occurred; truly preclinical detection will inevitably depend on the development of sensitive and specific biomarkers that have not yet been clearly standardised.

The NINDS-ADRDA criteria of 1984 have been recently revised by the National Institute on Aging and the Alzheimer's Association working group in an attempt to introduce diagnostic means of detecting the early stages of the disease (137,138). Similar efforts have been made by Dubois *et al.* (Table 3), who have proposed a set of core clinical diagnostic criteria and supportive criteria (including biomarkers), together with exclusion criteria (139,140).

Among the supportive criteria, considerable importance has been attributed to: i) MRI-detected atrophy of the mesial temporal structures; ii) abnormal cerebrospinal fluid biomarkers (particularly Abeta1-42, total tau and phosphorylated tau); iii) a specific metabolic pattern revealed by means of molecular neuroimaging,

including PET studies with Pittsburgh Compound B or other ligands of amyloid; and iv) familial genetic mutations. However, some criticisms have been made of this approach (141).

5.2.2 Familial AD

The great progress in the field of AD genetics led to the discovery and confirmation of three autosomal-dominant early-onset genes and a late-onset risk-factor; however, it is predicted that there are a number of other major AD loci (142).

Early-onset familial forms of AD (EOAD) with clinical symptoms appearing before the age of 65 account for less than 5% of cases. Most of them are linked to mutations in genes encoding APP, PS1 or PS2, and are inherited as an autosomal dominant trait with virtually complete penetrance. In addition, specific allelic variations of the APOE gene have been identified as risk factors for the disease (142). The APOE e4 genotype, which occurs in 16% of the population (143), is the main susceptibility gene identified in the human genome for both rare early-onset and sporadic late-onset AD (144).

Late-onset AD is characterised by a more multifaceted and interwoven pattern of genetic and non-genetic factors that is still poorly understood.

The most obvious difference between familial and sporadic cases of AD is the younger age at onset of subjects with EOAD mutations, especially PS1 mutations. In these cases, the first symptoms typically appear between the ages of 30 and 50 years, but some families have individuals affected in their twenties (145). Patients carrying genetic defects in the APP gene are usually older at the time of onset, typically in their fifties (range 45-60 years). EOAD related to PS2 mutations has a wide range of onset that also includes late-onset cases. The overall survival of patients with EOAD is similar to that of sAD patients, although the survival of PS1 mutation carriers may be slightly shorter (146).

EOAD cases often have an amnesic presentation similar to that seen in patients with sporadic disease, with the first deficits occurring in visual and verbal recall and recognition. The results of longitudinal studies of unaffected at-risk individuals suggest that the earliest neuro-psychometric findings involve a decline in verbal memory and performance IQ scores (147), with relatively preserved naming (148). However, atypical presentations (language deficits, behavioural abnormalities, focal neurological signs and symptoms) are much more common in familial cases, which should be considered a heterogeneous group of diseases as their clinical variability reflects their neuropathological and biochemical diversity. Myoclonus and seizures are both relatively more frequent, and myoclonus may be a harbinger of later seizures. Several PS1 mutations are variably associated with spastic paraparesis, and extrapyramidal and cerebellar signs. APP mutations clustered within the Abeta coding domain around positions 692-694 usually show a phenotype characterised by cerebral hemorrhage due to extensive amyloid angiopathy. Amyloid angiopathy and seizures are also common features in families carrying APP duplication (149).

6. DESCRIPTIONS OF THE MAIN CLINICO-PATHOLOGICAL ENTITIES

6.1. Sporadic Abeta amyloidosis

Sporadic CAA (sCAA) is more frequent than the hereditary forms and is a common clinico-pathological entity in the elderly. Cerebrovascular amyloid can be observed in approximately 10-40% of elderly brains and in 80% or more of brains with concomitant AD (150). When AD-related CAA is moderate to severe, there is a higher incidence of cerebral hemorrhages and ischemic lesions (151).

The relationship between CAA and cognitive impairment and dementia has been well established (127). In the MRC study, severe CAA was identified in 36.5% of the demented subjects and in only 7% of those without dementia (152). In the Honolulu-Asia Aging Study (HAAS), the co-presence of CAA and AD was associated with significantly worse cognitive test performance (153).

Stepwise decline can occur with both recurrent lobar hemorrhage and recurrent ischemia. The combination of ischemic and hemorrhagic events involving cortical-subcortical regions and the frequently associated leukoencephalopathy can induce severe cognitive decline in patients with CAA, in whom memory deficits, apathy and impaired executive function are often associated with psychomotor slowing, gait disturbances and focal neurological signs (116). Advanced white matter lesions are also a common finding. Severe white matter hypodensity on CT scans has been found to be associated with the presence of pre-ICH cognitive impairment (154), thus suggesting that white matter damage may explain at least some of the cognitive effects of advanced sCAA. An alternative clinical presentation involves relatively rapid cognitive decline (over weeks or months), seizures, dramatic white matter abnormalities on MRI scans, and evidence of CAA-related vasculitis or perivascular inflammation upon pathological examination (155,156); this presentation represents a potentially treatable form of the disease because it is frequently responsive to immunosuppressive therapy. Another important aspect of CAA-related inflammation is that it may be a naturally occurring form of the meningoencephalitis seen in some AD patients following Abeta42 immunisation (157).

Although the clinical picture, biochemical profile and neuropathological hallmarks of sAD are well defined in the current diagnostic criteria, a number of observations suggest that it may be heterogeneous and involve different disease subtypes. In this regard, the clinical, biochemical and neuropathological data should be systematically reviewed in order to identify and characterise the possible subtypes of sAD.

6.2. Hereditary Abeta amyloidosis

Early-onset familial forms of AD with clinical symptoms appearing before the age of 65 years account for less than 5-10% of cases (4). They are linked to mutations in three genes that encode APP (Figure 2), PS1, and PS2. A complete list of all of the reported APP genetic variants and the pertinent references can be found in the Alzheimer

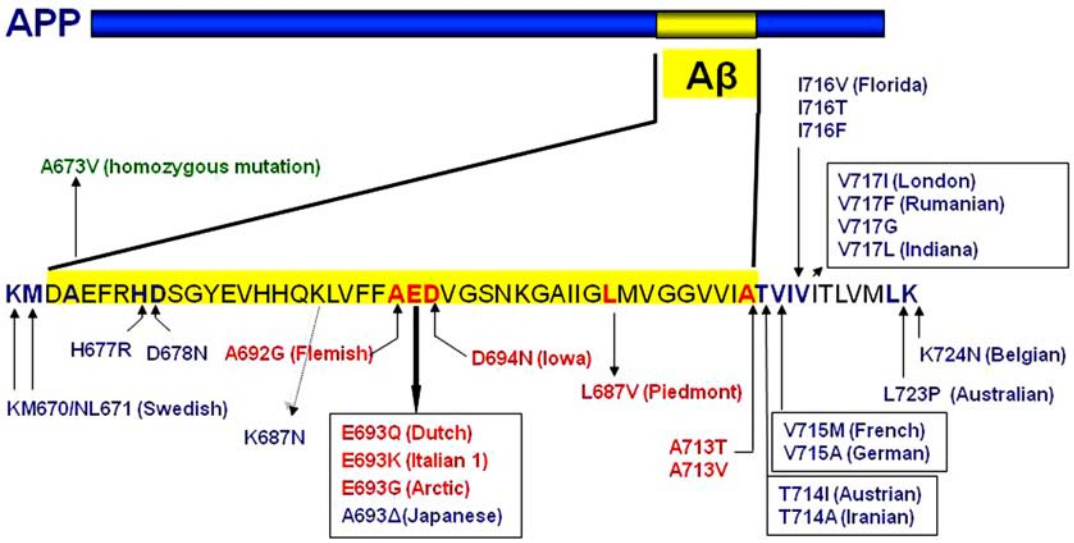

Figure 2. APP mutations associated with beta-amyloid amyloidosis. Mutations in the APP gene that cause beta-amyloid amyloidosis. In red, the genetic defects leading to "hereditary cerebral hemorrhage with amyloidosis-Dutch type" (HCHWA-D) or severe "cerebral amyloid angiopathy" (CAA). In blue, mutations leading to the classical AD clinico-pathological phenotype, or without distinctive clinical and neuropathological features. In green, the homozygous APP genetic defect associated to AD. The Figure does not include the duplications in the APP gene discussed in the text.

Disease and Frontotemporal Dementia Mutation Database (http://www.molgen.ua.ac.be/ADMutations/) and were reviewed in (7).

PS1 and PS2 mutations affect the levels of Abeta42 production by affecting the proteolytic activity of gamma-secretase, whereas amino acid changes in the APP molecule have different effects depending on the location of the mutated residue (91,158-162). As mentioned above, genetic variants within the Abeta sequence primarily affect the chemico-physical profile and aggregation capability of Abeta, and most of them are associated with CAA and ICH. However, amino acid substitutions flanking the Abeta region near the beta-secretase cleavage site modulate the rate of enzymatic processing of APP, thus increasing the production of Abeta42 and Abeta40 without affecting the Abeta42/Abeta40 ratio, and giving rise to a clinical and neuropathological phenotype that is similar to sporadic AD (7,163).

6.2.1. Hereditary cerebral hemorrhage with amyloidosis (HCHWA)

6.2.1.1. Dutch mutation

The Dutch variant was the first and is the best-described genetic defect associated with familial CAA. This autosomal dominant disorder is known as hereditary cerebral hemorrhage with amyloidosis - Dutch type (HCHWA-D) and caused by a G→C transversion at codon 693 of APP that gives rise to a glutamine to glutamic acid substitution at residue 22 of Abeta (E22Q) (164,165).

The disease has been identified in members of two large families in The Netherlands (166). The ApoE genotype does not modify the phenotypic expression of the E22Q mutation (167,168).

The co-existence of ischemic and (more frequently) hemorrhagic strokes is the dominant clinical symptom of HCHWA-D, usually leading to death or disability. Mean age at stroke onset is 50 years (range 39-76) (165). Cognitive involvement generally begins after the first stroke but, in some subjects, dementia is the first symptom and may develop before the first stroke or the brain imaging appearance of focal lesions. CAA itself is sufficient to cause dementia, and hemorrhages/infarctions may amplify and accelerate the development of cognitive deterioration (168). Epilepsy occurs in about half of the patients who suffer one or more strokes (156).

The recurrence of strokes may be easily demonstrated by imaging studies revealing recent and previous lobar cerebral hemorrhages (85%) or hemorrhagic/non-hemorrhagic infarctions (15%) that usually spare the frontal lobes, and small microbleeds leading to silent strokes and diffuse white matter damage, preferentially located in periventricular and/or subcortical occipital locations. These MRI findings are present in virtually all asymptomatic mutation carriers aged >40 years (166).

Neuropathological examination shows severe amyloid angiopathy, particularly of the cerebral and cerebellar meningeal arteries and cerebral cortical arterioles, as well as evidence of leukoencephalopathy (156). The blood vessels of the subcortical white matter are relatively spared. Amyloid deposition is associated with the loss of vascular smooth muscle cells, thickened vessel walls (often in a radial pattern), and a narrowed lumen. These changes often cause a re-arrangement of the vascular architecture such as "vessel-within-vessel" configurations (169,170), which correlate with the severity of CAA. Brain parenchymal Abeta deposition also occurs in HCHWA-D.

Plaque density tends to correlate inversely with age: younger patients have finer and more diffuse plaques, whereas older patients have fewer but denser plaques (168). Neurofibrillary degeneration is usually absent (Figure 1, panels M-P) (156). Abeta40 is the main component of vascular amyloid (171), but immunohistochemical and ultramicroscopic studies suggest that Abeta42 is the initially deposited Abeta species in the basement membrane of capillaries and the plasma membrane in the brain parenchyma (172,173).

6.2.1.2. Italian mutation

The genetic defect at the 693 codon of APP was identified in four apparently unrelated Italian families and consists of a G→A transition that gives rise to a glutamic acid to lysine substitution at residue 22 of Abeta (E22K). The mutation is associated with early-onset disease clinically characterised by the 10-20 year progression of recurrent strokes, mild cognitive decline and epilepsy, and neuropathologically marked by extensive deposits of Abeta in the walls of leptomeningeal and cortical vessels, diffuse parenchymal Abeta deposits lacking the tinctorial properties of amyloid, and the absence of mature plaques. Abeta40 isoform predominates in vessels, and Abeta42 in the parenchymal deposits. As in the Dutch cases, there is no tau-related pathology (Figure 1, panels M-P) (174).

6.2.2. Piedmont mutation

This APP genetic defect has been identified in association with CAA in a family from the Piedmont region of Italy. It consists of a G→C transition in APP codon 705 that gives rise to a valine to leucine substitution at Abeta residue 34 (175). Recurrent lobar hemorrhages onsetting between the ages of 50 and 72 years, and white matter abnormalities on CT and MRI scans are the most relevant clinical features. A global cognitive decline has also been observed. The neuropathological examination of two affected patients showed severe CAA in leptomeningeal, cerebral, and cerebellar vessels (156). Both Abeta40 and Abeta42 were present in vascular amyloid deposits. One distinctive neuropathological feature was the absence of parenchymal deposits and tau-related pathology (Figure 1, panels M-P).

6.2.3 FAD with severe CAA

6.2.3.1 Arctic mutation

An A→G transition at codon 693 of APP giving rise to a glycine for glutamic acid substitution at position 22 of Abeta (E22G) has been found in four generations of a family living in northern Sweden (156). The associated clinical picture is dominated by progressive cognitive impairment rather than clinically or neuroradiologically symptomatic strokes (176). Neuropathological reports describe moderate to severe cortical and leptomeningeal CAA, as well as SPs and neurofibrillary tangles (177). It has not yet been established whether CAA is the main hallmark of the neuropathological profile associated with this mutation.

6.2.3.2 Iowa mutation

A G→A transition at codon 694 of APP has been identified in an Iowa family. It induces a substitution of asparagine for aspartic acid at residue 23 of Abeta (178), and leads to a clinico-pathological profile that includes cognitive dysfunction, personality changes, myoclonic jerks and a short-stepped gait, without any episodes of clinically symptomatic ICH. However, small hemorrhages together with occipital calcifications (neuropathologically related to calcified amyloid-laden meningeal vessels) and subcortical leukoencephalopathy were identified by MRI. A second family from Spain carrying the same mutation showed symptomatic ICH in three out of four affected members (179), thus indicating that this mutation can lead to major cerebral hemorrhages in some settings. Post-mortem examination of two members of the Iowa pedigree revealed severe Abeta40-related amyloid angiopathy in meningeal and cortical vessels (180) and, although dense-cored plaques were rare, there were abundant neurofibrillary tangles as well as dystrophic neurites surrounding the amyloid-laden vessels.

6.2.3.3 Flemish mutation

A C→G transversion resulting in a substitution of glycine for alanine at codon 692 of APP (A21G) is known as the Flemish mutation and has been reported in two families from The Netherlands (181) and Great Britain (182). The clinical picture is characterised by recurrent lobar hemorrhages or progressive presenile dementia, and age at onset and death was between 35 and 61 years. The neuropathological profile is dominated by diffuse cortical atrophy and an abundance of vascular and parenchymal Abeta (primarily Abeta40) deposits, as well as neurofibrillary tangles. There was a predominance of atypically large dense cores plaques (average diameter 32 μm) accounting for 48% of total plaque size, which is different from other familial Abeta CAAs and sporadic AD plaques, which average 22 μm and have cores that account for only 16% of plaque size (183). Their apparent irradiation from affected vessels (184) suggests that AD pathology in this disease may be due to CAA.

6.2.3.4 A713T mutation

This APP genetic defect was found in an Italian family with autosomal dominant dementia and multiple strokes. Neuropathological examination of the proband revealed changes suggesting AD (the SPs were mainly of the neuritic type) with severe cerebral amyloid angiopathy and multiple infarcts. The distribution of the Abeta forms in the neuropil was unusual insofar as Abeta40 was relatively abundant in the SPs in comparison with sporadic AD (Figure 1, panels I-L) (115,185).

6.2.3.5 APP locus duplication

Different APP locus duplications have been recently identified in rare families with autosomal dominant early-onset AD and Abeta-related CAA (186,187), with remarkable inter- and intra-familial differences in clinical presentation and neuropathological phenotype, similar to those found in FAD patients with mutations in the presenilin 1 and presenilin 2 genes (188). In a study of 2006 by Cabrejo *et al.*, dementia was observed in 100% of cases, intracerebral hemorrhage (ICH) in 26%, and seizures in 57% of the 21 patients examined. The neuropathological findings in five cases demonstrated

the co-existence of typical AD changes and severe CAA, similar to those reported in the brains of Down's syndrome patients (189).

6.2.4. FAD associated with the homozygous A673V APP mutation

This mutation has been identified in an Italian family as a C-to-T transition at position 673 (APP770 numbering), giving rise to an Ala-to-Val substitution at residue 2 of Abeta. When it is homozygous, this genetic defect leads to early-onset dementia with behavioural changes and memory deficits in the prodromic phase, and severe cognitive deterioration with spastic tetraparesis at later stages. It is worth noting that the same mutation is not associated with disease in heterozygous carriers, even of advanced age (up to the tenth decade of life), as deduced on the basis of neuropsychological assessments (160), thus suggesting a recessive pattern of inheritance.

Neuropathological assessment of one patient carrying the A673V mutation in the homozygous state confirmed the diagnosis of AD, which had been suggested in vitam by a progressive decrease of CSF Abeta42 levels during the course of the disease (unpublished data). Nevertheless, the patient showed a distinct neuropathological profile (190) in terms of the morphological, structural and antigenic properties of Abeta deposits: i) they were very large; ii) they had an unusual perivascular arrangement defined by amyloid built up in the neuropil immediately surrounding the vessel wall, with a large compact core surrounded by a ring of bundles with a radial aspect and resembling long fringes (''fringed plaques''); iii) there was a distinctive pattern of Abeta species, with high Abeta40 content in both parenchymal and vascular deposits; and iv) there was a characteristic distribution involving unusual amyloid-targeted regions such as the cerebellum and the brainstem, with sparing of the striatum (unlike the hierarchical topographical sequence of brain involvement identified in sporadic AD) (191). The findings were unprecedented not only because of the Abeta40-positive deposits in the parenchyma and vessel walls, but also because of the absence of pre-amyloid deposits (Figure 1, panels Q-T) (190). This picture differs from that of any of the other cerebral Abeta amyloidoses reported so far.

The results of *in vitro* studies of cultured fibroblasts of the patient, transfected cells, and synthetic peptides carrying the A2V substitution indicate that the A673V APP mutation has two pathogenic effects: like the Swedish K670N/M691L double mutation, it shifts APP processing toward the amyloidogenic pathway, thus increasing Abeta production without altering the Abeta42/Abeta40 ratio, and it enhances the aggregation and fibrillogenic properties of Abeta (160).

Notably, co-incubation of the mutant peptide with equimolar concentrations of wild-type Abeta inhibits both fibrillogenesis and neurotoxicity, thus suggesting that the interaction of these Abeta species interferes with the nucleation-dependent polymerisation process. The dominant negative effect of this Abeta variant on amyloidogenesis may explain why heterozygous carriers do not develop the disease even in advanced age, and offers grounds for the development of therapeutic strategies based on modified Abeta peptides for both sporadic and familial AD (160).

6.2.5. FAD with less distinctive features

6.2.5.1 Swedish mutation

Among the genetic defects located near the beta-secretase APP cleavage site, the Swedish double mutation (K670N/M671L) (192) greatly increases the production of Abeta40 and Abeta42 (193,194) in cell lines (193,195) and cultured fibroblasts (196) as result of enhanced beta-secretase activity, without changing the Abeta40/Abeta42 ratio (175). This is consistent with findings in the brain tissue of patients carrying the Swedish mutation (197), although the Abeta peptides terminating at residue 42 (i.e. Abeta1-42 and Abeta11-42) are the predominant species in plaques, the total amount of Abeta40 and Abeta42/43 is similar to that observed in sporadic AD, as is the Abeta40/Abeta42 ratio (159). The clinical and pathological phenotype associated with this mutation does not differ substantially from that of sporadic AD (7).

6.2.5.2 E693Δ mutation

A deletion mutation in the APP gene (E693delta) giving rise to an Abeta variant lacking Glu at position 22 has recently been found in two Japanese pedigrees showing AD-type dementia (161). The lack of neuropathological information concerning these cases makes it difficult to collocate this genetic defect in the group of AD-related or CAA-related APP mutations. The findings of studies of cultured cells indicated enhanced intracellular accumulation of Abeta oligomers, and the results of *in vitro* studies of synthetic peptides also suggest increased Abeta oligomerisation in the absence of amyloid fibril formation. Moreover, the non-fibrillogenic properties of E22D were paralleled by a very low amyloid positron emission tomography signal in the patient's brain using Pittsburgh Compound B, indicating synaptotoxic Abeta oligomers as the probable cause of the dementia associated with this genetic defect (161,162).

6.2.5.3 Other mutations

A group of mutations occurring in close proximity to the gamma-secretase cleavage sites (at the C-terminus of Abeta) typically increase the production of Abeta42 and/or lower the levels of Abeta40, thus replicating the effects caused by mutations in the presenilin genes (175,194). As a result, the Abeta42/Abeta40 ratios is increased in all of these mutants, as indicated by studies of transfected cells (198). This cluster of APP mutations includes A713V; T714A (Iranian); T714I (Austrian); V715M (French); V715A (German); I716V (Florida); I716T; V717I (London); V717L (Indiana); V717F (Rumanian); V717G; L723P (Australian), and K724N (Belgian). The clinical picture associated with these mutations includes the occurrence of focal neurological deficits, myoclonus, seizures, behavioural disturbances and personality changes throughout the progression of the disease (even in the early stages), which makes it quite difficult to diagnose AD. In addition to the usual AD-

related hallmarks, neuropathological examination often reveals the presence of amyloid angiopathy and vascular changes, but these are under-represented in comparison with hbetaCAA cases, especially in the case of mutations causing a decrease in Abeta40 peptide levels, or the presence of Lewy body-like pathology (199).

In conclusion, the spectrum of clinical presentations associated with pathogenic APP mutations is expanding and now includes: i) cerebral amyloid angiopathy with intracerebral hemorrhage occurring in the mutations associated with CAA; ii) the classical predominantly amnesic clinical phenotype occurring in the mutations flanking the N- and C-termini of the Abeta sequence, evolving towards a global cognitive deterioration not unlike that seen in most sporadic AD cases; iii) the "intermediate" phenotypes typically associated with the Flemish mutation and APP duplications, which lead to cerebral amyloid angiopathy in association with memory-led cognitive decline; and iv) the clinical phenotype characterised by pure progressive amnesia which has been more recently identified in patients carrying APP mutations at codon 717 (200).

6.2.6 Non-APP familial AD mutations

AD clinical phenotypes are also observed in patients with mutations in non-APP genes. Depending on the genes involved, some of these familial cases (PS mutations) show the deposition of Abeta peptides, whereas others show the deposition of unrelated amyloid molecules with clinical phenotypes of dementia and/or hemorrhagic stroke.

6.2.6.1 Presenilin mutations

PS mutations are associated with the presence of familial forms of AD, and account for about 80% of the cases of early-onset AD (4). Almost 200 different mutations in PS1 gene have been found in independent families so far, and only 25 mis-sense mutations in the PS2 gene (http://www.molgen.ua.ac.be/ADMutations/). The phenotype associated with each genetic variant depends on the gene, the type of mutation, and the affected transmembrane domain (201). All of the PS mutations are linked to autosomal dominant AD onsetting usually before the age of 60 years and almost complete penetrance (202). The youngest ages of onset are seen in families with PS1 mutations, and typically fall within the range of 35-55 years. APP mutations tend to give rise to symptom onset at an age of 40-65 years, and PS2 mutations at an age of 40-70 years (203).

Families with PS1 gene mutations are characterised by marked allelic heterogeneity (204). These mutations generally lead to greater deposition of total Abeta and Abeta42 (but not Abeta40) in the brain in comparison with sporadic AD. There is also considerable heterogeneity in the neuropathological profiles of patients with different mutations, and although some lead to the predominantly parenchymal deposition of Abeta in the form of diffuse and cored plaques, others (typically those located after codon 200 of the PS1 gene) lead to predominantly vascular deposition, with severe amyloid angiopathy. Although the clinical phenotype is in most cases similar to late-onset AD, variability occurs even among family members carrying the same mutation (4,205,206).

FAD associated with PS mutations typically presents with the insidious impairment of episodic memory, which may be comparable to the amnesic mild cognitive impairment, prodromic to sporadic AD. However, atypical presentations involving other cognitive domains before memory and/or language and behavioural abnormalities occur in patients carrying PS mutations more often than in those with sporadic AD (203-207). Myoclonus and seizures can appear early in the disease course and may precede cognitive symptoms. PS1 mutations may be associated with spastic paraparesis, extrapyramidal signs or cerebellar ataxia and. Albeit rarely, these may be the presenting features. Spastic paraparesis is often associated with PS1 exon 9 deletions, and the characteristic histopathological features known as cotton wool plaques are frequently seen in these cases (208). Severe cerebellar Abeta deposition has been observed in the case of some PS1 mutations (P117A, S170F) (Figure 1, panels E-H) (205,209,210). PS1 cases show a potent inflammatory response around plaques (211) and have higher levels of inflammatory mediators in soluble brain tissue extracts, possibly due to the loss of presenilin regulation of inflammation (212). These plaques with increased inflammation have been called inflammatory plaques (IP) and are found in the cortical regions of cases with PS1 and APP mutations (114).

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