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Parenchymal and vascular Aβ-deposition and its effects on the degeneration of neurons and cognition in Alzheimer's disease

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Abstract

The deposition of the amyloid β-protein (Aβ) is one of the pathological hallmarks of Alzheimer's disease (AD). Aβ-deposits show the morphology of senile plaques and cerebral amyloid angiopathy (CAA). Senile plaques and vascular Aβ-deposits occur first in neocortical areas. Then, they expand hierarchically into further brain regions. The distribution of Aβ plaques throughout the entire brain, thereby, correlates with the clinical status of the patients. Imaging techniques for Aβ make use of the hierarchical distribution of Aβ to distinguish AD patients from non-AD patients. However, pathology seen in AD patients represents a late stage of a pathological process starting 10–30 years earlier in cognitively normal individuals. In addition to the fibrillar amyloid of senile plaques, oligomeric and monomeric Aβ is found in the brain. Recent studies revealed that oligomeric Aβ is presumably the most toxic Aβ-aggregate, which interacts with glutamatergic synapses. In doing so, dendrites are presumed to be the primary target for Aβ-toxicity. In addition, vascular Aβ-deposits can lead to capillary occlusion and blood flow disturbances presumably contributing to the alteration of neurons in addition to the direct neurotoxic effects of Aβ. All these findings point to an important role of Aβ and its aggregates in the neurodegenerative process of AD. Since there is already significant neuron loss in AD patients, treatment strategies aimed at reducing the amyloid load will presumably not cure the symptoms of dementia but they may stop disease progression. Therefore, it seems to be necessary to protect the brain from Aβ-toxicity already in stages of the disease with minor neuron loss before the onset of cognitive symptoms.

Keywords: amyloid β-protein • Alzheimer • amyloid plaques • cerebral amyloid angiopathy • dendritic degeneration

Introduction

Alzheimer's disease (AD) is a slowly progressing neurodegenerative disease that leads to dementia [1]. Pathologically, neuron loss and synapse loss occur and provide a neuropathological correlative for dementia [2–4]. The histopathological hallmarks that characterize AD are senile plaques, neurofibrillary tangles (NFTs) and neuropil threads (NTs) [1, 5, 6] (Fig. 1).

NFTs and NTs consist of abnormally phosphorylated τ-protein that aggregates to paired-helical filaments forming neurofibrillary material [7–10]. These aggregates occur in the soma of nerve cells (NFTs) as well as in neurites (NTs) [1, 7, 8] (Fig. 1). Tangle-bearing neurons degenerate during a number of years resulting in neuronal death [8, 11, 12]. The first step in this process is the occurrence of abnormally phosphorylated τ-protein in the cell soma of nerve cells before aggregation and tangle formation [8]. 'Tombstone'-tangles are NFTs remaining in the neuropil after neuronal death [5].

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Senile plaques (synonymous with amyloid plaques), on the other hand, are extracellular deposits of amyloid-material in the neuropil [1, 5]. This amyloid material consists of fibrillar aggregates of amyloid β-protein (Aβ) (Fig. 1) [13]. Aβ is a 39–43 amino acid protein, which is derived from the amyloid precursor protein (APP) by β- and γ-secretase cleavage (Fig. 2A) [14].

Cerebral amyloid angiopathy (CAA), *i.e.* the deposition of Aβ in cerebral blood vessels, is frequently found in AD. Vascular amyloid deposits are most frequently found in leptomeningeal and cortical vessels (Fig. 1H and I) [15, 16].

This review focuses on the role of parenchymal and vascular Aβ-deposition for the degeneration of neurons in the AD patient as well as in mouse models.

The deposition of Aβ

The deposition of Aβ in the human brain starts in the neocortex and then expands hierarchically into further brain regions representing different phases of Aβ-deposition (Fig. 2B, Table 1) [17–19]. These phases of Aβ-deposition correlate with the expansion of neurofibrillary changes as represented by the Braak stages (Fig. 2B) [17, 18]. More importantly, the expansion of Aβ-deposition into further brain regions also correlates well with the degree of dementia given by the CDR-score similar to that of neurofibrillary tangles as represented by the Braak-stage (Fig. 3A and B) [17]). A similar hierarchical expansion of vascular Aβ-deposition was found [20]. Three stages of CAA can be distinguished (Fig. 2B, Table 1) and correlate with the phases of Aβ-plaque-deposition and the degree of dementia (Fig. 3C) [20]).

Since there is a good correlation between the expansion of Aβ-deposition in the brain and dementia it is obvious that the overall distribution of Aβ, including diencephalic, brain stem and cerebellar regions, is related to the development of dementia [17, 21, 22]. The amount of Aβ-deposition in a given cortical or hippocampal region, *i.e.* the Aβ-load or semiquantitative plaque scores obtained in these regions, does not show significant differences among different degrees of dementia [23–26], between control cases with high amounts of AD-related pathology and AD cases [27–31] and among the levels of brain atrophy [32]. However, when comparing all non-demented cases with AD patients in a sample of 177 elderly autopsy cases between 20 and 99 years of age a significant difference in the Aβ-load was observed (Fig. 3D).

The deposition of Aβ in different areas of the brain results in the development of different types of Aβ-deposits, which can be summarized as amyloid plaques or senile plaques (for review see: [5, 33, 34]). In spite of region-specific plaque-types the most important distinction is made between neuritic and non-neuritic plaques. According to the Consensus criteria of the National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease neuritic plaques are those which exhibit Aβ-deposits in association with dystrophic neurites containing argyrophilic or thioflavin S-positive aggregates, *i.e.* τ-aggregates [35, 36]. Other authors also include plaques exhibiting APP-positive dystrophic neurites negative for τ into the group of neuritic plaques [34, 37]. To allow a distinction between these different types of neuritic plaques with only one being relevant for the diagnosis of AD [35] it has been suggested to distinguish APP-type neuritic plaques without τ-aggregates from PHF-type neuritic plaques [33, 38, 39]. In addition to these morphological variations the biochemical composition varies among different plaque types as well [40–44].

All types of Aβ-deposits are seen in demented as well as in non-demented patients [18]. For example, diffuse plaque types are the first to be deposited in the neocortex of non-demented individuals [18, 19, 40, 42, 45, 46]. They also occur in a similar pattern within the cerebellum and the brain stem when these regions become newly involved in AD cases [17, 47]. Thus, all types Aβ-deposits presumably represent AD-related Aβ-deposition and do not represent morphological alterations restricted to normal aging. Arguments favouring this hypothesis are: 1) there are cases even in very high ages who have not developed Aβ-pathology [48] (Fig. 4A); 2) mouse models overexpressing only APP show a similar sequence of Aβ-deposition as human beings indicating that the sequence of Aβ-deposition described in the human brain represents the course of Aβ-deposition starting with the first cortical plaques in non-demented individuals and coming to an end with the full-blown pattern of Aβ-deposition in AD cases [33, 49] (Fig. 2); and 3) advanced Aβ-deposition was related to a reduction of neuronal connectivity in the human brain [50] as well as in animal models [51, 52].

The current criteria for the diagnosis of AD define AD as dementia associated with mid – late stage NFT and neuritic plaque pathology [35]. In these stages, significant neuronal and synaptic loss is seen as well [4, 53].

APP-presenilin 1 double transgenic mouse models do not show a similar pattern of Aβ-deposition as seen in the human brain or in APP single transgenic mice [54]. The co-expression of presenilin 1 under control of a HMG-CoA-promoter may explain the differences reported in the pattern of Aβ-deposition in these mice in comparison to the human brain and to mice overexpressing only APP driven by a Thy-1 promoter [33, 54].

Neurotoxicity of Aβ

Synaptic and neuron loss are features of the pathological picture in AD cases [2–4]. The use of animal models overexpressing APP leading to the deposition of Aβ allowed the confirmation of synaptic loss as a potential result from Aβ-aggregation [55]. Neuron loss has only been observed in one APP-transgenic mouse model whereas others did not exhibit this pathology [49, 56]. APP-presenilin 1-double transgenic mice showed similar neuron loss [57]. However, mutant presenilin 1 is not only responsible for Aβ-production but also involved in other neuronal cell death mechanisms

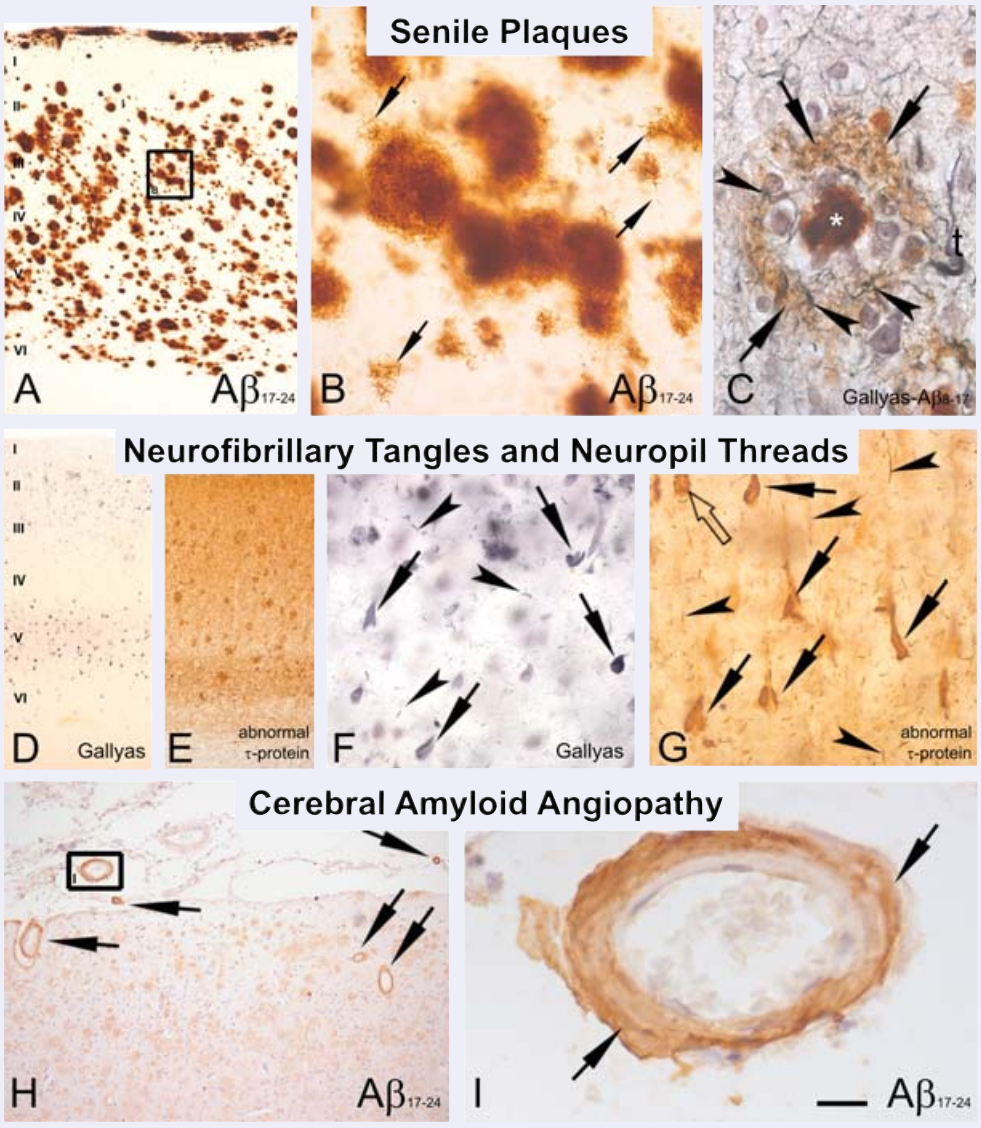


Fig. 1 (**A–C**) Senile plaques in the temporal neocortex of AD cases. All layers are occupied by senile plaques, which contain Aβ as demonstrated by immunolabelling with an antibody raised against $A\beta_{17-24}$ (4G8). In the higher magnification, the fibrillar nature of the Aβ deposits can be seen (arrows in **B**). The 'needle-like' appearance characterized even diffuse Aβ-deposits (arrows in **B**; [152]). **C** shows a cored neuritic plaques stained in a combination of a Gallyas-silver staining for neurofibrillary material (black) and anti-$A\beta_{8-17}$ (6F3D) immunohistochemistry (brown). The amyloid core (*) is seen in the center of the plaques surrounded by a halo of diffuse Aβ-deposits (arrows). Here dystrophic neurites occur, which contain argyrophilic neurofibrillary material (arrowheads) indicative for neuritic plaques [35]. Adjacent to the cored neuritic plaques there is a NFT (t). (**D, E)** NFTs and NTs in the temporal cortex of an AD case. NFTs are most prominent in the pyramidal cell layers III and V. NFTs and neuropil threads contain fibrillar material detected be the Gallyas silver methods (**D**). These fibrils consist of aggregates of abnormally phosphorylated τ-protein (**E**). With the antibody against abnormal τ-protein not only Gallyas-positive fibrils are marked but also non-aggregated abnormal τ-protein (**E**; [8]). (**F, G)** NFTs (arrows) and NTs (arrowheads) in the subiculum/ CA1 region at the higher magnification level. Both structures are stained with the Gallyas silver method and an antibody directed against abnormal τ-protein (AT-8). The neuron indicated with the open arrow shows accumulation of abnormal τ-protein in the pre-tangle status. (**H, I)** Cerebral amyloid angiopathy in the parietal cortex of an AD patient. There are Aβ-deposits in leptomeningeal and cortical vessels (arrows in **H**). The higher magnification shows the destruction of the vessel wall by Aβ-deposits that replace smooth muscle cells of the media (arrows in **I**). The numbers I–VI indicate the cortical layers in **A** and **D**. Calibration bar in **I** valid for: **A** = 300 μm; **B** = 30 μm; **C, I** = 15 μm; **D**, **H** = 150 μm; **E** = 370 μm; **F, G** = 50 μm.

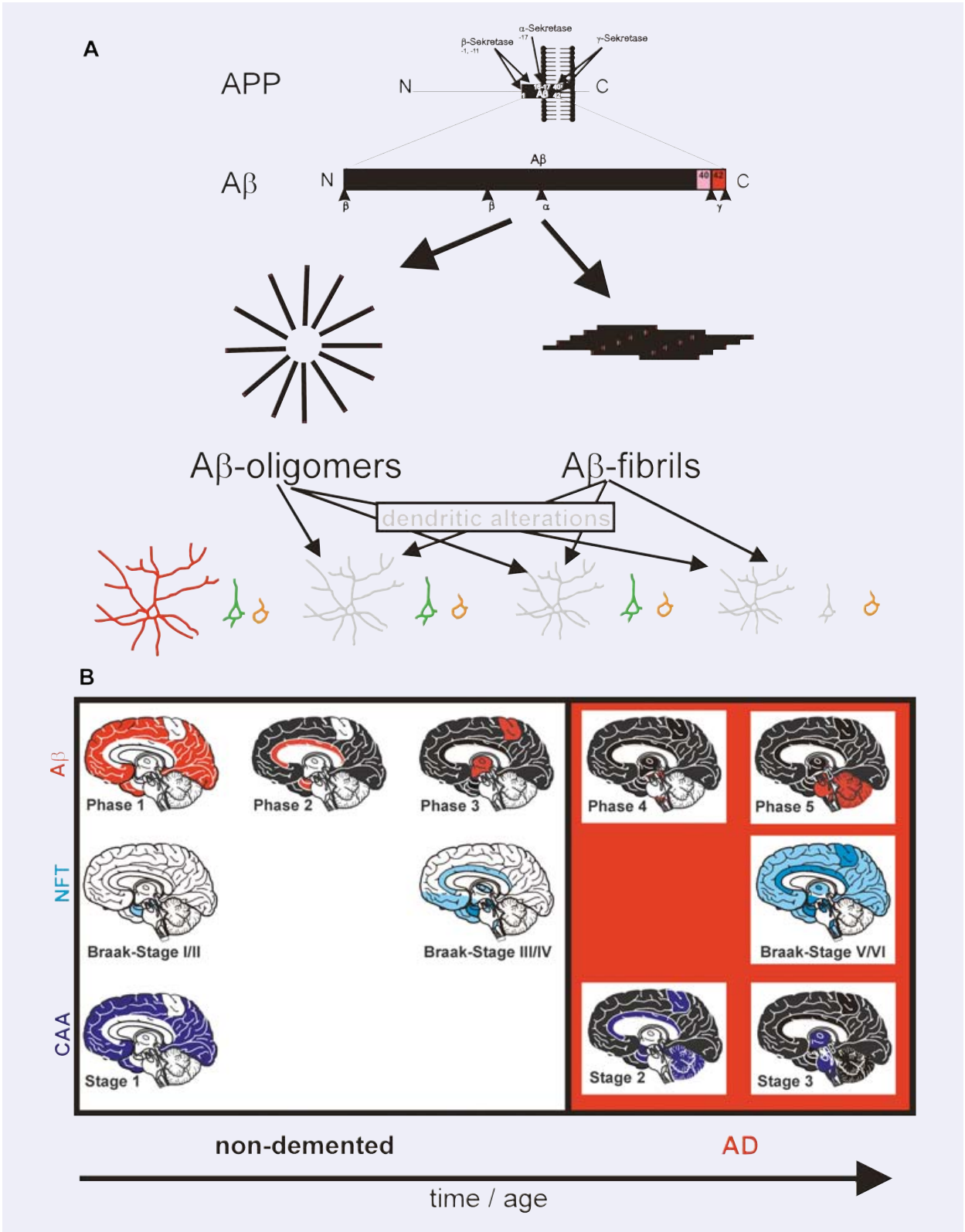


Fig. 2 Schematic representation of Aβ generation, aggregation, deposition in the brain and its relation to neuronal changes. (**A**) Aβ is the cleavage product of β- and γ-secretase cleavage of the amyloid precursor protein (APP) [14]. It is a 39–43 amino acid protein. $Aβ_{40}$ and $Aβ_{42}$ are the major forms [40]. Aβ forms oligomers [64, 70] and fibrils [13, 86]. It is not clear whether oligomeric Aβ can form fibrils. However, the hypothesis that a conformational switch of Aβ is decisive for either fibril formation or oligomer formation has been supported by a recent study [153]. Fibrillar and oligomeric Aβ alter neurons [51, 52, 67, 69, 72–74, 154]. An interaction between Aβ-oligomers with glutamatergic synapses has been demonstrated [65–67]. Moreover, neurons with a prominent, highly ramified dendritic tree are more vulnerable than neurons exhibiting only single dendrites indicating a selective vulnerability of different types of neurons depending on the dendritic tree anatomy [51]. Neurons in grey represent degenerated neurons whereas those painted in colour are intact. (**B**) The hierarchical expansion of Aβ-deposits throughout the brain follows five phases [17] (areas marked in red are newly involved in Aβ-plaque deposition, areas marked in black are not newly involved in Aβ-plaque pathology but exhibit Aβ-plaques): First Aβ-plaques occur in the neocortex (phase 1). Then they expand into allocortical regions (phase 2), the basal ganglia and the diencephalon (phase 3), and into the midbrain and the medulla oblongata (phase 4). In the fifth and final phase the pons and the cerebellum also exhibit Aβ-deposits. The regions of the medial temporal lobe exhibit a similar sequence of Aβ-plaque deposition in its subfields that strongly correlates with these phases [17, 18] (Table 1). The expansion of Aβ-plaque pathology goes along with that of NFTs as indicated by the Braak-stages [19] (Braak-stages: areas marked in light blue are newly involved in NFT pathology, areas marked in dark blue are not newly involved in NFT pathology but exhibit NFTs). End stage Aβ- and NFT-pathology (Aβ-phase 4, 5; Braak stage V, VI) is associated with the clinical picture of AD whereas early stages (Aβ-phase 1–2; Braak stage I-III) of the disease are usually not clinically apparent [17, 125]. Phase 3 and Braak-stage IV are often associated with AD but are also found in non-demented cases [17]. Parallel with the deposition of Aβ-plaques and the generation of NFTs CAA develops (CAA-stages: areas marked in scarab blue are newly involved in vascular Aβ deposition, areas marked in black are not newly involved in vascular Aβ pathology but exhibit CAA). First vascular Aβ-deposits occur in the first stage of CAA in leptomeningeal and parenchymal vessels of neocortical regions. In the second stage, allocortical regions, the midbrain and the cerebellum become involved (Table 1). In stage 3, CAA is also seen in the pons, the medulla oblongata, the basal ganglia and the thalamus [20]. AD cases most frequently exhibit late stage CAA, *i.e.* CAA-stages 2 and 3 as well (see also Fig. 3C). Animal experiments indicated that the phases of Aβ-deposition represent a time course of the development of this pathology [33]. Together with the time-dependent degeneration of distinct types of neurons these data strongly suggest that Aβ triggers the process of AD-related neurodegeneration. This hypothesis is strongly supported by the finding that Aβ-triggers τ-pathology in APP-τ-transgenic mice [155, 156] and after injection into the brain of τ-single transgenic mice [157].

not depending on Aβ-aggregation [58–60]. Mouse models carrying a presenilin mutation may, therefore, not be ideally suited for studying Aβ-induced neurodegeneration.

Despite the lack of neuron loss most APP-transgenic mouse models showed 'cognitive symptoms' [61–63]. Recently, Aβ-oligomers have been found in the AD and APP-transgenic mouse brain [64]. Aβ-oligomers interact with glutamatergic synapses [65–67] and inhibit long-term potentiation [68, 69]. The injection of dodecameric Aβ-oligomers, *i.e.* 'Aβ*56' into the brain induced transient 'cognitive symptoms' in the treated animals [70]. However, it is not clear whether such transient 'clinical' changes have a distinct morphological correlative or not. The E693Δ Mutation of the APP gene was recently identified in a Japanese pedigree of AD patients [71]. The mutant Aβ peptide showed enhanced oligomerization but no fibrillization [71] arguing in favour of Aβ-oligomers as a toxic Aβ form at least in the brain of the diseased APP E693Δ family members.

In APP-transgenic mice neuritic/dendritic degeneration has been observed in association with amyloid plaques as well as in the absence of Aβ-deposits [51, 52, 72–74]. Moreover, there is a hierarchical vulnerability of different types of neurons to Aβ-aggregates similar to that seen in the human brain [51]. Interestingly, those neurons with a prominent dendritic tree are most susceptible to Aβ-induced neurodegeneration while those with only few and small dendrites remained unaffected [51]. The vulnerability of neurons with a prominent dendritic tree fits with the concept of dendritic/synaptic alterations by extracellular Aβ-oligomers [65–67, 69].

The role of intraneuronal Aβ, especially Aβ-oligomers in the context of neuronal degeneration is not clear. To date it is obvious that Aβ is produced by neurons [75, 76] and that it can accumulate within neurons [75]. Some of these neurons also showed features of synaptic degeneration [77] and contained oligomeric Aβ-aggregates [78]. However, Aβ also occurs in the extracellular space of APP-transgenic mouse models and the human brain. Thus, reuptake of Aβ and/ or Aβ-oligomers may also explain intracellular Aβ and oligomeric Aβ-aggregates. The occurrence of Aβ within multivesicular bodies [77] – multivesicular bodies are formed during the maturation from early to late endosomes and, thereby, represent organelles of the endocytic pathway [79] – also argues in favour of endocytosis of amyloid or amyloidogenic material. Moreover, amyloid plaques can also be formed in mice producing Aβ by extracellular cleavage of a BRI-Aβ42 construct [80]. Further studies are required to clarify the role of intracellular Aβ.

Contribution of CAA to the degeneration of neurons

A total of 80–100% of the AD patients exhibit CAA [16, 81–83] (for review see: [81, 83, 84]). The overall expansion of CAA is more advanced in AD cases when compared to non-AD controls and it correlates with the Braak stages, the phases of Aβ-deposition, and the degree of dementia (Figs. 2 and 3) [20, 81, 85].

Table 1:

A: Disease stage at which senile plaques and CAA appear in the different regions of the human brain		
Brain region	Senile plaques	CAA
Frontal cortex	Phase 1	Stage 1
Parietal cortex	Phase 1	Stage 1
Temporal cortex	Phase 1	Stage 1
Occipital cortex	Phase 1	Stage 1
Hippocampal formation	Phase 2	Stage 2
Insular cortex	Phase 2	Stage 2
Cingulate cortex	Phase 2	Stage 2
Entorhinal cortex	Phase 2	Stage 2
Amygdala	Phase 2	Stage 2
Hypothalamus	Phase 3	Stage 2
Thalamus	Phase 3	Stage 3
Basal ganglia	Phase 3	Stage 3
Basal forebrain nuclei	Phase 3	Stage 3
Midbrain	Phase 4	Stage 2
Medulla oblongata	Phase 4	Stage 3
Pons	Phase 5	Stage 3
Cerebellum	Phase 5	Stage 2

The phases of senile plaque deposition indicate in which phase a given region is involved in Aβ-plaque pathology [17]. Likewise the stage of CAA indicates in which stage a given region is involved in CAA [20]. The grey shades indicate the correlating severities of Aβ-phases and CAA-stages.

B: Disease stage at which senile plaques appear in the different subdivisions of the medial temporal lobe	
MTL region	Senile plaques
Temporal cortex	Phase 1
Entorhinal cortex (except pre-α layer)	Phase 2
CA1/ Subiculum	Phase 2
Presubicular region	Phase 3
Molecular layer of the Fascia Dentata	Phase 3
MTL: white matter	Phase 3
CA4	Phase 4
Pre-α layer of the entorhinal cortex	Phase 4

The expansion of Aβ-deposition in the different subfields of the medial temporal lobe correlates with that in the entire brain [17]. The table depicts which medial temporal lobe subfields are involved in which phase of Aβ-deposition in the medial temporal lobe [18]. The grey shades indicate the correlating severities of Aβ-deposition in the medial temporal lobe.

Pathologically, CAA is characterized by the deposition of Aβ in leptomeningeal, cortical and subcortical cerebral vessels [86]. In addition to arteries and veins capillaries can be affected as well [87]. The deposition of Aβ in the vessel wall leads to destruction of smooth muscle cells in the vessel wall and finally to a fragile vessel wall [88]. In doing so, rupture of such fragile, CAA-affected vessels can cause intracerebral hemorrhage [15, 16, 88].

Aβ deposition in capillaries distinguishes two types of CAA: CAA-type 1 = CAA with capillary CAA; and CAA-type 2 = CAA without capillary involvement [89]. Other authors suggested that capillary involvement represents most severe CAA but not a distinct type [90]. The strong association of the apolipoprotein E (APOE) ε4-allele with the capillary type as well as to the occurrence of capillary CAA in all stages of parenchymal Aβ-deposition [89] argue in favour of distinct types of CAA. Recently, CAA-induced capillary occlusion has been found to explain blood flow disturbances in an APP-transgenic mouse model [91]. Moreover, other authors described functional deficits in these mice [92] indicating an affection of those thalamic nuclei, which exhibit capillary CAA with capillary occlusion [91]. Imaging studies revealed that hypoperfusion is well known in the brains of AD patients [93–95]. In the light of these results CAA-related capillary occlusion is one possible morphological correlative for hypoperfusion. Ischaemic lesions were usually not found near capillary occlusions in human and transgenic mouse brain [91]. However, cerebral infarction is a well-known complication of CAA [15, 16].

These studies suggest that CAA with capillary occlusion contributes to neuronal dysfunction in AD in addition to direct neurotoxic effects of Aβ. This conclusion is supported by the predominant occurrence of capillary CAA (CAA-type 1) in AD cases [83, 90, 96] (Fig. 5).

Clinical impact of Aβ and its therapeutic possibilities

Since Aβ plays a key role in the pathogenesis of AD and since Aβ is a driving force for neuritic and synaptic degeneration it is a primary target for therapy. Today, blocking Aβ-production by β- or γ-secretase inhibition [97–100], and active and passive vaccination against Aβ [101–103] appear to be promising strategies.

Inhibitors for the γ-secretase often also block Notch-processing and, therefore, go along with severe side effects, *i.e.* alteration

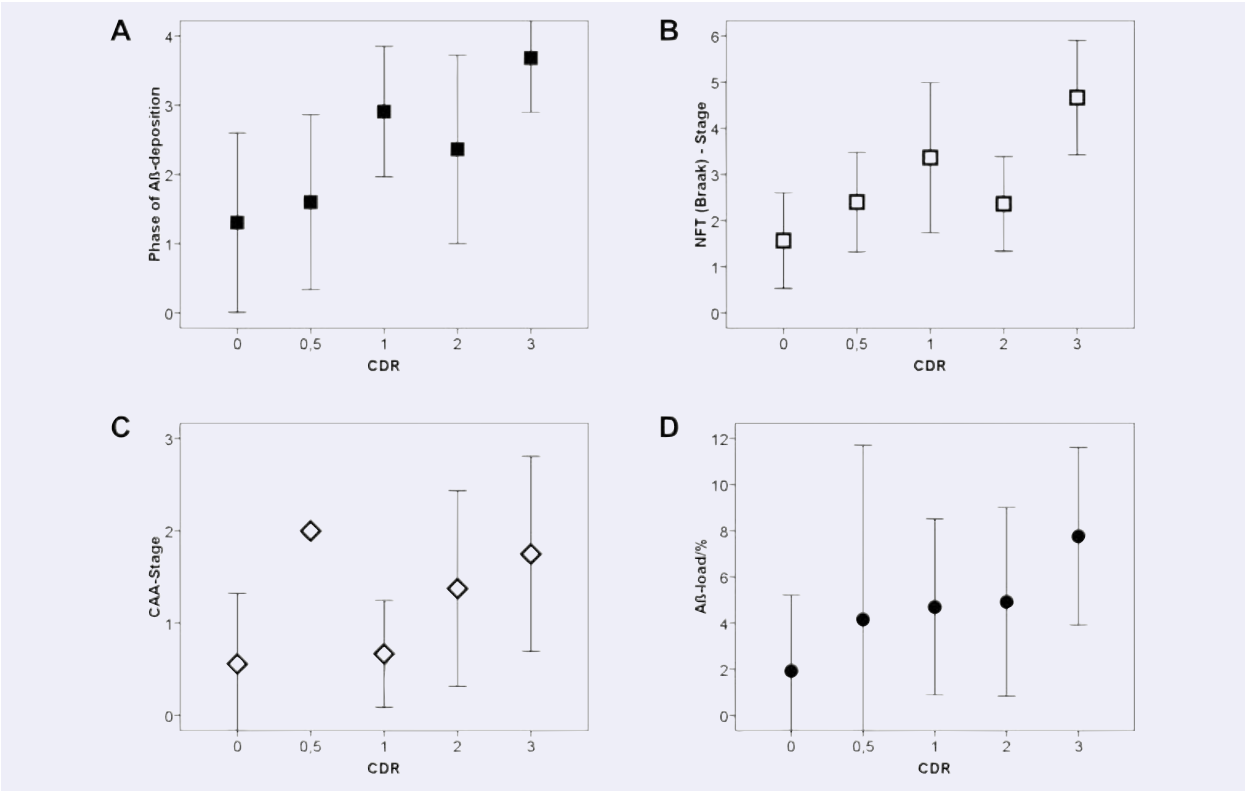
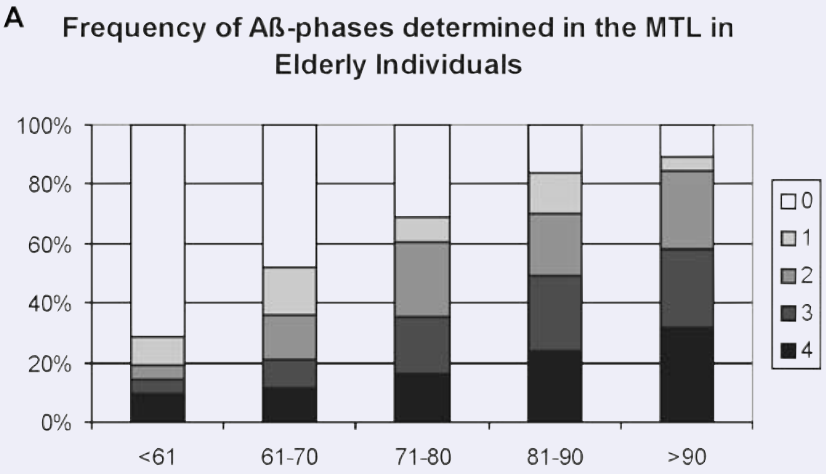


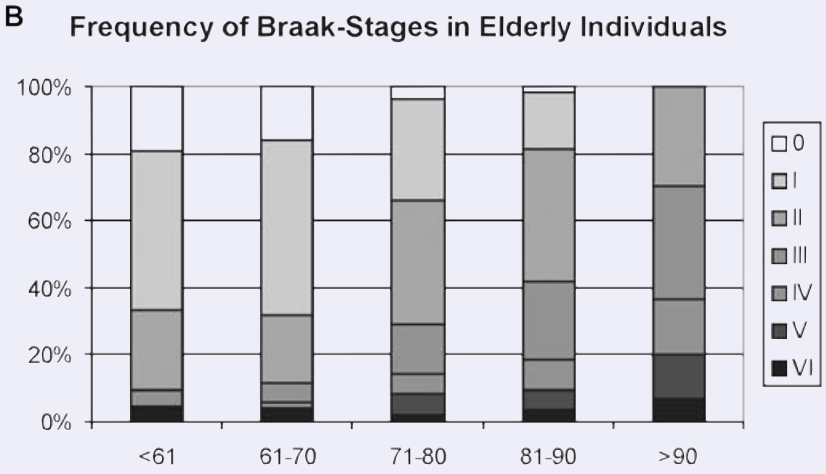
Fig. 3 Expansion of Aβ-plaque pathology in the medial temporal lobe (Phase of Aβ-deposition) [18] (**A**), NFTs (Braak stage [19]) (**B**), and CAA (CAA-stage) [20] (**C**) in the brain of non-demented and demented patients. The degree of dementia is given by the CDR-score. AD cases (cases with CDR-scores of 1–3; other causes of dementia were excluded) showed more widely distributed Aβ-plaques (**A**; $n = 214$ cases; Student's t-test $P < 0.001$), NFTs (**B**; $n = 214$ cases; Student's t-test $P < 0.001$), and CAA (**C**; $n = 67$ cases; Student's t-test $P < 0.001$) than non-demented cases with CDR-scores of 0. MCI patients with a CDR-score of 0.5 [158, 159] showed intermediate stages. (**D**) The Aβ-load (obtained as described earlier [44]) in the temporal neocortex was also higher in AD cases than in non-demented individuals with a CDR-score of 0 ($n = 177$ cases; Student's t-test $P < 0.001$). Mean values are presented and the standard deviation is indicated by the bars.

of lymphopoiesis and intestinal cell differentiation [104]. Newly developed γ-secretase inhibitors are sought to block the γ-secretase specific for APP-processing and to avoid Notch-related side effects [97, 100]. In higher doses γ-secretase inhibitors are capable of promoting carcinogenesis [105]. Absence of BACE-1 in BACE-1-knockout/ APP-transgenic mice reduced the Aβ-load in comparison to APP-transgenic mice with endogenous BACE-1 activity [106–108]. In addition, the β-secretase (BACE-1) function is also involved in synaptic plasticity and myelination [107, 109, 110]. Thus, so far β- and γ-secretase inhibitors are not clinically proven and the side effects reported for such inhibitors imply a very careful and critical testing of such drugs in the future.

Non-steroidal anti-inflammatory drugs like ibuprofen and indomethacin also modulate the γ-secretase cleavage of APP [111]. Although these drugs are well proven and widely used in rheumatology, their impact for the treatment of AD is controversially discussed [112–116].

Vaccination strategies are successful in APP-transgenic mice [101–103]. Both, active and passive vaccination, lead to a reduction of the Aβ-load and improve the performance of APP-transgenic mice in cognitive tests [101–103]. Active vaccination has already been tested in human beings. Although active vaccination leads to a reduction of Aβ in the brain [117–119] and to a slower progression of cognitive decline [120] severe side effects, *i.e.* aseptic meningoencephalitis occurred in 6% of the treated patients [121]. There was no evidence so far that Aβ-vaccination improved cognition of demented patients [122]. The aseptic meningoencephalitis after Aβ-vaccination is a T-cell-mediated inflammatory reaction induced by the dominant T-cell epitope $A\beta_{10–24}$ [123]. The development of vaccines sparing such epitopes appears to be very promising [123]. A further side effect observed after passive immunization in animal models was an increased frequency of hemorrhages due to CAA [124]. An option to avoid such side effects triggered by vascular Aβ-deposition could be to start with





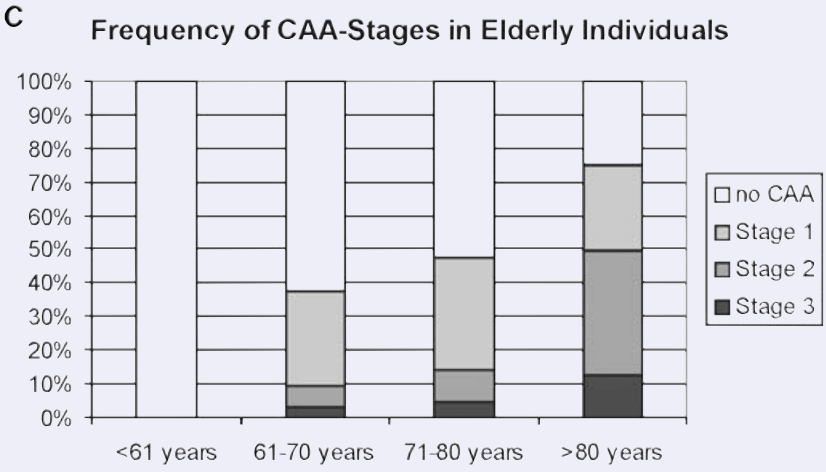


Fig. 4 (**A**) The frequency of patients with Aβ-deposits increases with age. Only 11% of the patients older than 90 years of age were free of Aβ-deposits in a sample of 506 autopsy cases. Accordingly, the prevalence of higher phases of Aβ-deposition as observed in the medial temporal lobe [18] also increases with age. (**B**) Similar to the deposition of Aβ NFTs occur in most individuals older than 90 years. In our sample, there was no one free of NFTs at this age. The percentage of cases with NFTs in cases younger than 71 years of age was strikingly higher than that of those with Aβ-plaques. This result is in line with previously published samples [48]. (**C**) In parallel with the increasing frequency of Aβ-deposits and NFTs in elderly people CAA occurs more often in advanced ages and the prevalence of higher stages increases when compared with younger age groups. This is demonstrated in a sample of 88 autopsy cases (reproduced with kind permission from [83]).

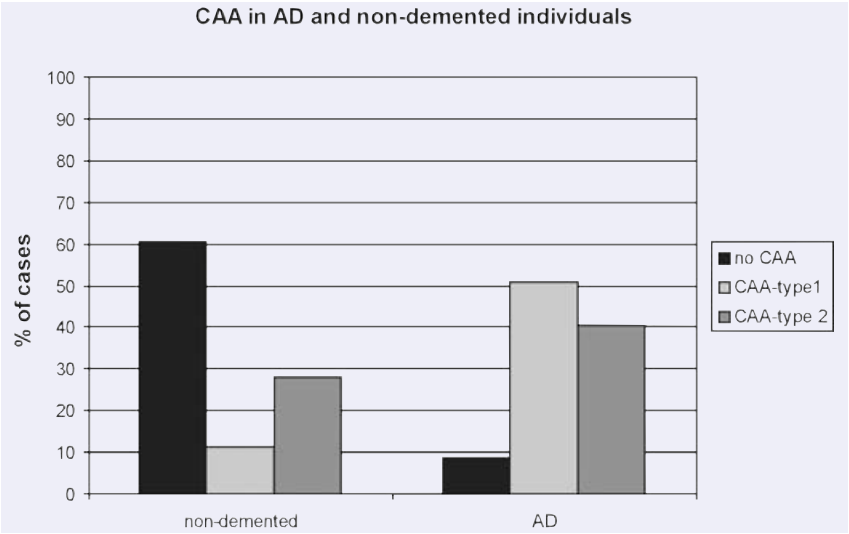


Fig. 5 Prevalence of CAA and its subtypes in AD and age-matched non-demented control cases. In non-demented controls, most individuals were free of CAA (60.4%). Controls with CAA most frequently exhibited CAA-type 2 lacking capillary involvement (28.2%). Only 11.4% of the controls showed capillary CAA (CAA-type 1). On the other hand, capillary CAA (CAA-type 1) was found in 51% of the AD cases. Only 40% of the AD cases exhibited CAA-type 2 and 9% were free of CAA. These data confirm that capillary CAA is frequent in AD [96].

Aβ-vaccination already in asymptomatic patients without CAA [122]. In animal models, this therapeutic setting has been shown to be superior compared with beginning at later stages [102]. Taken together, vaccination strategies appear to be very promising but this treatment strategy still needs to be successfully tested in human beings for its therapeutic effects and drug safety.

As already described above, Aβ-deposits occur not only in AD patients but also in cognitively normal individuals [19, 45, 46]. The hierarchical expansion of neurofibrillary and Aβ-pathology throughout the brain starts with the first senile plaques in the neocortex and the first NFTs in the transentorhinal region, the basal nucleus of Meynert and the dorsal raphe nucleus in non-demented individuals [12, 17, 19, 125–127] (Fig. 2B, Table 1). In APP-transgenic mice a similar sequence of Aβ-deposition has been reported as in the human brain [33] arguing in favour of the hypothesis that overall Aβ-deposition in AD is the end stage of a pathological process starting with the first neocortical plaques. The strong correlation between NFT distribution as represented by the Braak-stage and the expansion of Aβ-deposition throughout the brain further supports this notion [17]. Following this hypothesis, preclinical AD starts in non-demented patients approximately 20–30 years before the onset of dementia [48, 128] without major neuronal loss. In doing so, these patients with the earliest signs of AD pathology would be the best candidates for a protection from further Aβ-toxicity, *e.g.* by vaccination.

The identification of such early, asymptomatic stages of AD is not possible today before autopsy. However, autopsy studies revealed that initial stages of AD-related pathology prevail in most individuals older than 60 years of age [48] (Fig. 4). The prevalence of advanced stages of AD-related pathology increases with age [48] (Fig. 4). The prevalence of end stage AD-related pathology, thereby, correlates with the clinical picture of AD (Fig. 3A–C). The increase of early stages precedes that of end stages by 20–30 years [48, 128]. Extrapolation of the prevalence of AD with increasing life expectancy predicts a dramatic rise of symptomatic AD patients in the future (Fig. 4). This demographic prediction strongly underscores the importance to protect people from AD whenever applicable before symptoms arise.

Imaging techniques using specific markers, *e.g.* the brain amyloid ligand 11C-labelled Pittsburgh Compound B (PIB), have been developed to detect Aβ in the brain [129–131]. These techniques already allow a good distinction between AD and non-AD patients [129, 130]. The pattern of Aβ detected with these imaging methods is similar to that seen after autopsy [17, 19, 129, 132–134]. However, reagents like PIB are not specific for binding only on Aβ-deposits [135]. Other protein aggregates may cross-react with this dye [135]. Moreover, PIB is a thioflavin S analogue [136] and, in doing so, does not detect all diffuse Aβ-deposits that are seen immunohistochemically [134]. Therefore, today it is not possible to identify clinically normal patients with Aβ-plaques with these imaging techniques in a sensitive and specific manner but one may expect that such techniques will be improved during the next years allowing a much more sensitive detection of Aβ-plaques in the future even in non-demented individuals.

Genetic effects on Aβ-deposition are numerous [137, 138]. However, only four genes are widely proven for their influence on AD pathology: APP, PS1, PS2 and APOE [139–145]. APP, PS1 and PS2 gene mutations are all associated with familial forms of AD [139, 140, 143–146], whereas the APOE ε4 allele is associated with sporadic AD and CAA [141, 147–149]. Screening for APP, PS1 and PS2 mutations can help to detect family members at risk for AD [146]. For sporadic AD, APOE genotyping is often determined in demented patients but its diagnostic value is limited [150]. APOE ε4 carriers develop clinical and neuropathological changes of AD usually earlier than non-carriers [150]. Age and gender, thereby, additionally modify its effects on the neuropathological pattern of neurofibrillary tangle and senile plaque distribution [151].

Conclusions

The deposition of Aβ is a slowly progressive process starting in the neocortex. Further brain regions become involved in a hierarchical sequence. The spatial distribution and the expansion of Aβ-plaques and CAA are, thereby, correlated. Aβ-aggregates, *i.e.* Aβ-oligomers and/ or fibrillar Aβ aggregates induce, on the one hand, neuritic, especially dendritic degeneration and, on the other hand, capillary occlusion leading to cerebral blood flow disturbances. In doing so, there are two major mechanisms in which Aβ alters the brain of AD-patients: neurotoxicity of Aβ-aggregates and vessel occlusion. Therefore, therapeutic strategies should not focus only on protecting the neurotoxic effects of Aβ but also on the reduction of vascular deposits and an improvement of cerebral blood flow. Most importantly, AD-pathology starts in non-demented individuals a long time before the onset of clinical symptoms. Such a long preclinical course of AD is ideally suited for starting protective therapies such as vaccination. The aim would be the prevention of clinical AD or the prolongation of the preclinical stage. In the light of the demographically predictable increase of patients developing AD, it seems to be better to protect people from getting AD rather than to treat demented patients with the limitations of an already irrecoverable altered brain.

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