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 correlate 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 β-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 β-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].
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, 44, 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 Aβ17–24 (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-Aβ4–17 (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.
not depending on 
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 correlate 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 fibrillation [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 endocytotic 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].

![Fig. 2 Schematic representation of Aβ generation, aggregation, deposition in the brain and its relation to neuronal changes.](image-url)
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) e4-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 correlate 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...
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 Aβ10–24 [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]).
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 neurological changes of AD usually earlier than non-carriers [150]. Age and gender, thereby, additionally modify its effects on the neuropsychological pattern of neurofibrillary tangle and senile plaque deposition [151].

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].
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, neurotic, 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.

References

1. Alzheimer A. Ueber eine eigenartige Erkrankung der Hirnrinde. Allg Zschr Psych 1907; 64: 146–8.
2. DeKosky ST, Scheff SW. Synapse loss in frontal cortex biopsies in Alzheimer’s disease: correlation with cognitive severity. Ann Neurol. 1990; 27: 457–64.
3. Masliah E, Mallory M, Hansen L, DeTeresa R, Allford M, Terry R. Synaptic and neuritic alterations during the progression of Alzheimer’s disease. Neurosci Lett. 1994; 174: 67–72.
4. Terry RD, Peck A, DeTeresa R, Schechter R, Horoupian DS. Some morphometric aspects of the brain in senile dementia of the Alzheimer type. Ann Neurol. 1981; 10: 184–92.
5. Duyckaerts C, Dickson DW. Neuropathology of Alzheimer’s disease. In: Dickson D, editor. Neurodegeneration: the molecular pathology of dementia and movement disorders. Basel: ISN Neuropath Press; 2003. pp. 47-65.
6. Braak H, Braak E. Neuropil threads occur in dendrites of tangle-bearing nerve cells. Neuropathol Appl Neurobiol. 1988; 14: 39-44.
7. Bancher C, Brunner C, Lassmann H, Budka H, Jellinger K, Wiche G, Seitelberger F, Grundke-Iqbal I, Iqbal K, Wisniewski HM. Accumulation of abnormally phosphorylated tau precedes the formation of neurofibrillary tangles in Alzheimer’s disease. Brain Res. 1989; 477: 90-9.
8. Braak E, Braak H, Mandelkow EM. A sequence of cytoskeleton changes related to the formation of neurofibrillary tangles and neuritophyl threads. Acta Neuropathol. 1994; 87: 554-67.
9. Grundke-Iqbal I, Iqbal K, Quinlan M, Tung YC, Zaidi MS, Wisniewski HM. Microtubule-associated protein tau. A component of Alzheimer paired helical filaments. J Biol Chem. 1986; 261: 6084-9.
10. Grundke-Iqbal I, Iqbal K, Tung YC, Quinlan M, Wisniewski HM, Binder LI. Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. Proc Natl Acad Sci USA. 1986; 83: 4913-7.
11. Bancher C, Brunner C, Lassmann H, Budka H, Jellinger K, Seitelberger F, Grundke-Iqbal I, Iqbal K, Wisniewski HM. Tau and ubiquitin immunoreactivity at different stages of formation of Alzheimer neurofibrillary tangles. Prog Clin Biol Res. 1989; 317: 837-48.
12. Sassi C, Schultz C, Thal DR, Rub U, Arai K, Braak E, Braak H. Evolution of Alzheimer’s disease-related cytoskeletal changes in the basal nucleus of Meynert. Acta Neuropathol. 2000; 100: 259-68.
13. Masters CL, Simms G, Weinman NA, Multhaup G, McDonald BL, Beyreuther K. Amyloid plaque core protein in Alzheimer disease and Down syndrome. Proc Natl Acad Sci USA. 1985; 82: 4245-9.
14. Haass C, Koo EH, Mollen A, Hung AY, Selkoe DJ. Targeting of cell-surface beta-amyloid precursor protein to lysosomes: alternative processing into amyloid-bearing fragments. Nature. 1992; 357: 500-3.
15. Mandybur TI. Cerebral amyloid angiopathy; the vascular pathology and complications. J Neuropathol Exp Neurol. 1986; 45: 79-90.
16. Vinters HV. Cerebral amyloid angiopathy. In: Barnett HJM, Mohr JP, Stein BM, Yatsu FM, editors. Stroke. Pathophysiology, diagnosis and management. 2nd ed. New York: Churchill Livingstone; 1992. pp. 821-51.
17. Thal DR, Rub U, Orantes M, Braak H. Phases of Abeta-deposition in the human brain and its relevance for the development of AD. Neurology. 2002; 58: 1791-800.
18. Thal DR, Rub U, Schultz C, Sassi C, Ghebremedhin E, Del Tredici K, Braak E, Braak H. Sequence of Abeta-protein deposition in the human medial temporal lobe. J Neuropathol Exp Neurol. 2000; 59: 733-48.
19. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. Acta Neuropathol. 1991; 82: 239-59.
20. Thal DR, Ghebremedhin E, Orantes M, Westlinder ID. Vascular pathology in Alzheimer’s disease: correlation of cerebral amyloid angiopathy and arteriosclerosis / lipohyalinosis with cognitive decline. J Neuropathol Exp Neurol. 2003; 62: 1287-301.
21. Gold G, Kovari E, Corte G, Herrmann FR, Canuto A, Bussiere T, Hof PR, Bouras C, Giannakopoulos P. Clinical validity of A beta-protein deposition staging in brain aging and Alzheimer disease. J Neuropathol Exp Neurol. 2001; 60: 946-52.
30. Lue LF, Kuo YM, Roher AE, Brachova L, Woodward M, Merory J, Tochon-Danguy H, O’Keefe G, Klunk WE, Mathis CA, Price JC, Masters CL, Villemagne VL. Imaging beta-amyloid burden in aging and dementia. *Neurology.* 2007; 68: 1718–25.

31. Dickson DW, Cristal HA, Mattiace LA, Masur DM, Blau AD, Davies P, Yen SH, Aronson MK. Identification of normal and pathological aging in prospectively studied nondemented elderly humans. *Neurobiol Aging.* 1992; 13: 179–89.

32. Josephs KA, Whitwell JL, Ahmed Z, Shiung MM, Weigand SD, Knopman DS, Boeve BF, Parisi JE, Petersen RC, Dickson DW, Jack CR Jr. Beta-amyloid burden is not associated with rates of brain atrophy. *Ann Neurol.* 2008; 63: 204–12.

33. Thal DR, Capellito-Zarate E, Del Tredici K, Braak H, Ghebremedhin E. Apolipoprotein E co-localizes with newly formed amyloid beta-protein (Abeta)-deposits lacking immunoreactivity against N-terminal epitopes of Abeta in a genotyping-dependent manner. *Acta Neuropathol.* 2005; 110: 459–71.

34. Arriagada PV, Marzloff K, Hyman BT. Distribution of Alzheimer-type pathologic changes in nondemented elderly individuals matches the pattern in Alzheimer’s disease. *Neurology.* 1992; 42: 1681–8.

35. Price JL, Davis PB, Morris JC, White DL. The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer’s disease. *Neurobiol Aging.* 1991; 12: 295–312.

36. Markesbery WR, Trojanowski JQ, Kowal D, Liang Y, Yang Z, McCusker K, Fox A. Full-length amyloid-beta (1–42) and amino-terminally modified amyloid-beta N3(pE), in senile plaques. *Neuron.* 1995; 14: 457–66.

37. Arion E, Saire C, Delorme A, Delacourte A, Sette A, Caselli R, Masur DM, Braak H, Yen SH, Aisen PS. Neuritic alterations but no axonal disconnection in senile plaque types in Alzheimer’s disease: signif- icance in plaque evolution. *J Neurochem.* 1995; 64: 276–81.

38. Dickson DW. The pathogenesis of senile plaques. *J Neurochem.* 1997; 66: 321–39.

39. Wang D, Munoz DG. Qualitative and quan-titative differences in senile plaque dystrophic neurites of Alzheimer’s disease and normal aged brain. *J Neurochem.* 1995; 64: 548–56.

40. Iwatsubo T, Odaka A, Suzuki N, Mizusawa H, Nukina N, Ihara Y. Visualization of A beta 42(43) and A beta 40 in senile plaques. *Acta Neuropathol.* 2008; 115: 175–83.

41. Saito TC, Yamao-Harigaya W, Iwatsubo T, Kawashima S. Amino- and carboxyl-terminal heterogeneity of beta-amyloid peptide deposits in human brain. *Neurosci Lett.* 1996; 215: 173–6.

42. Fiala JC. Mechanism of amyloid plaque pathogenesis. *Acta Neuropathol.* 2007; 114: 551–71.

43. Price JL, Davis PB, Morris JC, White DL. The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer’s disease. *Neurobiol Aging.* 1991; 12: 295–312.

44. Arriagada PV, Marzloff K, Hyman BT. Distribution of Alzheimer-type pathologic changes in nondemented elderly indivi-duals matches the pattern in Alzheimer’s disease. *Neurology.* 1992; 42: 1681–8.

45. Price JL, Davis PB, Morris JC, White DL. The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer’s disease. *Neurobiol Aging.* 1991; 12: 295–312.

46. Lalowski M, Golabek A, Lemere CA, Selkoe DJ, Wisniewski HM, Beavis RC, Franzione P, Wisniewski T. The “non- amyloidogenic” p3 fragment (amyloid beta17–42) is a major constituent of Down’s syndrome cerebellar premyloid. *J Biol Chem.* 1996; 271: 33623–31.

47. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol Aging.* 1997; 18: 351–7.

48. Irizarry MC, Soriano F, McNamara M, Page KJ, Schenk D, Games D, Hyman BT. Abeta deposition is associated with neur- opil changes, but not with overt neuronal loss in the human amyloid precursor pro-tein V717F (PDAPP) transgenic mouse. *J Neurosci.* 1997; 17: 7053–9.

49. Thal DR, Capellito-Zarate E, Del Tredici K, Braak H, Ghebremedhin E. Apolipoprotein E co-localizes with newly formed amyloid beta-protein (Abeta)-deposits lacking immunoreactivity against N-terminal epitopes of Abeta in a genotyping-dependent manner. *Acta Neuropathol.* 2005; 110: 459–71.
52. Wu CC, Chawla F, Games D, Rydel RE, Freedman S, Schen D, Young WG, Morrison JH, Bloom FE. Selective vulnerability of dentate granule cells prior to amyloid deposition in PDAPP mice: digital morphometric analyses. Proc Natl Acad Sci USA. 2004; 101: 7141–6.

53. Gomez-Isla T, Price JL, McKeel DW Jr, Morris JC, Gwondon JH, Hyman BT. Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer’s disease. J Neurosci. 1996; 16: 4491–500.

54. Langui D, Girardot N, El Hachimi KH, Allingnant B, Blanchard V, Pradier L, Duyckaerts C. Subcellular topography of neuronal Abeta peptide in APPxPS1 transgenic mice. Am J Pathol. 2004; 165: 1465–77.

55. Hsia AY, Masliah E, McConlogue L, Yu SQ, Tatsuno G, Hu K, Kholodenko D, Malekna RC, Nicoll RA, Mucke L. Plaque-independent disruption of neural circuits in Alzheimer’s disease mouse models. Proc Natl Acad Sci USA. 1999; 96: 3228–33.

56. Calhoun ME, Wiederhold KH, Abramski D, Phinney AL, Probst A, Sturchler-Pierrat C, Staufenbiel M, Sommer B, Jucker M. Neuron loss in APP transgenic mice. Nature. 1998; 395: 755–6.

57. Schmitz C, Rutten BP, Pielen A, Schater S, Wirths O, Tremp G, Czech C, Blanchard V, Multhaup G, Rezaie P, Kor H, Steinbusch HW, Pradier L, Bayer TA. Hippocampal neuron loss exceeds amyloid plaque load in a transgenic mouse model of Alzheimer’s disease. Am J Pathol. 2004; 164: 1495–502.

58. Guo Q, Sopher BL, Furukawa K, Pham DG, Robinson N, Martin GM, Mattson MP. Alzheimer’s presenilin mutation sensitizes neural cells to apoptosis induced by trophic factor withdrawal and amyloid beta-peptide: involvement of calcium and oxyradicals. J Neurosci. 1997; 17: 4212–22.

59. Wolozin B, Iwasaki K, Vito P, Ganjej JK, Lacana E, Sunderland T, Zhao B, Kusiat JW, Wasco W, D’Adamo L. Participation of presenilin 2 in apoptosis: enhanced basal activity conferred by an Alzheimer mutation. Science. 1996; 274: 1710–3.

60. Chui DH, Tanahashi H, Ozawa K, Ikeda S, Checler F, Ueda O, Suzuki H, Araki W, Inoue H, Shirato K, Takahashi K, Gallays F, Tabira T. Transgenic mice with Alzheimer presenilin 1 mutations show accelerated neurodegeneration without amyloid plaque formation. Nat Med. 1999; 5: 560–4.

61. Nalbantoglu J, Tirado-Santiago G, Lahsaini A, Poirier J, Goncalves O, Verge G, Momoli F, Welter SA, Massicotte G, Julien JP, Shapiro ML. Impaired learning and LTP in mice expressing the carboxy terminus of the Alzheimer amyloid precursor protein. Nature. 1997; 387: 500–5.

62. Chen G, Chen KS, Knox J, Inglis J, Bernard A, Martin SJ, Justice A, McConlogue L, Games D, Freedman SB, Morris RG. A learning deficit related to age and beta-amyloid plaques in a mouse model of Alzheimer’s disease. Nature. 2000; 408: 975–9.

63. Moran PM, Higgins LS, Cordell B, Moser PC. Age-related learning deficits in transgenic mice expressing the 751-amino acid isoform of human beta-amyloid precursor protein. Proc Natl Acad Sci USA. 1995; 92: 5341–5.

64. Kayed R, Head E, Thompson JL, Mcintyre TM, Milton SC, Cotman CW, Glabe CG. Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis. Science. 2003; 300: 486–9.

65. Lacor PN, Buniel MC, Chang L, Fernandez SJ, Gong Y, Viola KL, Lambert MP, Velasco PT, Bigio EH, Finch CE, Kraftt KL, Klein WL. Synaptic targeting by Alzheimer’s-related amyloid beta oligomers. J Neurosci. 2004; 24: 10191–200.

66. Shankar GM, Bloodgood BL, Townsend M, Walsh DM, Selkoe DJ, Sabatini BL. Natural oligomers of the Alzheimer amyloid-beta protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. J Neurosci. 2007; 27: 2866–75.

67. Roselli F, Tirard M, Lu J, Hutzler P, Dotti CG, Unckel K, Klein WL. A specific amyloid-beta protein assembly disrupts postsynaptic density-95 at glutamatergic synapses. J Neurosci. 2005; 25: 1181–3.

68. Bertram L, Holtzman DM, Bacskai BJ, Hyman BT. Rapid appearance and local toxicity of amyloid-beta plaques in a mouse model of Alzheimer’s disease. Nature. 2008; 451: 720–4.

69. Tsai J, Gurtzendler J, Duff K, Gan WB. Fibrillar amyloid deposition leads to local synaptic abnormalities and breakage of neuronal branches. Nat Neurosci. 2004; 7: 1181–3.

70. Lees S, Koh MT, Kellinek L, Kayed R, Glabe CG, Yang A, Gallagher M, Ashe KH. A specific amyloid-beta protein assembly in the brain impairs memory. Nature. 2006; 440: 352–7.

71. Tomiyama T, Nagata T, Shimada H, Teraoka R, Fukushima A, Kanemitsu H, Takuma H, Kuwano R, Imagawa M, Ataka S, Wada Y, Yoshioka E, Nishizaki T, Watanabe Y, Mori H. A new amyloid beta variant favoring oligomerization in Alzheimer’s-type dementia. Ann Neurol. 2008; 63: 377–87.

72. Meyer-Luehmann M, Spires-Jones TL, Prada C, Garcia-Alloza M, de Calignon A, Rozkalne A, Koenigsknig-Talbbo J, Holtzman DM, Bacskai BJ, Hyman BT. Neuronal abeta42 accumulation in human brain. Am J Pathol. 2000; 156: 15–20.

73. Hartmann B, Bieger SC, Bruhl B, Tienari PJ, Ida N, Allosp D, Roberts GW, Masters CL, Dotti CG, Unsicker K, Beyreuther K. Distinct sites of intracellular production for Alzheimer’s disease A beta40/42 amyloid peptides. Nat Med. 1997; 3: 1016–20.

74. Takahashi RH, Milner TA, Li F, Nam EE, Edgar MA, Yamaguchi H, Beal MF, Xu H, Greengard P, Reiner NR. Intraneuronal Abeta42 accumulation in multi-vesicular bodies and is associated with synaptic pathology. J Neurosci. 2002; 22: 4557–74.

75. Wang HW, Pasternak JF, Kuo H, Ristic H, Lambert MP, Chromy B, Viola KL, Klein WL, Stine WB, Kraftt KL, Teraoka R, Fukushima A, Kanemitsu H, Takuma H, Kuwano R, Imagawa M, Ataka S, Wada Y, Yoshioka E, Nishizaki T, Watanabe Y, Mori H. A new amyloid beta variant favoring oligomerization in Alzheimer’s-type dementia. Ann Neurol. 2008; 63: 377–87.

76. Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. The molecular biology of nucleic acids. 2nd ed. New York: Garland Publishing; 1989.
of the cell. 4th ed. New York: Garland Science; 2002.
80. McGowan E, Pickford F, Kim J, Onstead L, Eriksen J, Yu C, Skipper L, Murphy MP, Beard J, Das P, Jansen K, DeLucia M, Lin W-L, Dolios G, Wang R, Eckman CB, Dickson DW, Hutton M, Hardy J, Golde T. Aβ42 is essential for parenchymal and vascular amyloid deposition in mice. Neuron. 2005; 47: 191–9.
81. Attems J. Sporadic cerebral amyloid angiopathy: pathology, clinical implications, and possible pathomechanisms. Acta Neuropathol. 2005; 110: 345–59.
82. Joachim CL, Morris JH, Selkoe DJ. Clinically diagnosed Alzheimer’s disease: autopsy results in 150 cases. Ann Neurol. 1988; 24: 50–6.
83. Thai DR, Griffin WST, De Vos RA, Ghebremedhin E. Cerebral amyloid angiopathy and its relationship to Alzheimer’s disease. Acta Neuropathol. 2008; 115: 599–609.
84. Revesz T, Ghiso J, Lashley T, Plant G, Joachim CL, Morris JH, Selkoe DJ, Rostagno A, Frangione B, Holton JL. Association between severe cerebral amyloid angiopathy and its effect on cognitive decline are influenced by Alzheimer amyloid angiopathy and its relationship to Alzheimer’s disease. J Neurosci. 2003; 23: 8231–6.
85. Foster NL, Chase TN, Mansi L, Brooks R, Fedio P, Patronas NJ, Di Chiuro G. Cortical abnormalities in Alzheimer’s disease. Ann Neurol. 1984; 16: 649–54.
86. Johnson NA, Jahng GH, Weiner MW, Miller BL, Chui HC, Jagust WJ, Gorno-Tempini ML, Schuff N. Pattern of cerebrohypoperfusion in Alzheimer disease and mild cognitive impairment measured with arterial spin-labeling MR imaging: initial experience. Radiology. 2005; 234: 851–9.
87. Meguro K, Blaiotz X, Kondoh Y, Le Mestruc C, Baron JC, Chavoux O. Neocortical and hippocampal glucose hypometabolism following neurotoxic lesions of the entorhinal and perirhinal cortices in the non-human primate as shown by PET. Implications for Alzheimer’s disease. Brain. 1999; 122: 1519–31.
88. Attems J, Jellinger KA. Only cerebral capillary amyloid angiopathy correlates with Alzheimer pathology—a pilot study. Acta Neuropathol. 2004; 107: 83–90.
89. Barten DM, Guss VL, Corsa JA, Loo A, Li T, Wen H, Brayton C, Laird FM, Ma G, Morgan D, Diamond DM, Gottschall PE, Vonsattel JP, Anderson JJ, Loy JK, Denton R, Jaquet MA, Biere AL, Curran E, Brigham EF, Chen KS, Friedman SB, Games D, Johnson-Wood K, Lee M, Zeller M, Liu W, Motter R, Sinha S, Staufenbiel M, Baird A, Hatcher J, Hope C, Gordon M, Arendash GW. A beta peptide vaccination prevents memory loss in an animal model of Alzheimer’s disease. Nature. 2000; 408: 979–82.
90. Morgan D, Diamond DM, Gottschall PE, Ugen KE, Dickey C, Hardy J, Duff K, Jantzen P, DiCarlo G, Wilcock D, Connor K, Hatcher J, Hope C, Gordon M, Arendash GW. A beta peptide vaccination prevents memory loss in an animal model of Alzheimer’s disease. Nature. 2000; 408: 979–82.
91. Wang GT, Mantra D, Poulet FM, Zhang Q, Josien H, Bara T, Engstrom L, Pinzon-Ortiz M, Fine JS, Lee HJ, Zhang L, Higgins GA, Parker EM. Chronic treatment with the gamma-secretase inhibitor LY-411,575 inhibits beta-amyloid peptide production and alters lymphopoiesis and intestinal cell differentiation. J Biol Chem. 2004; 279: 12876–82.
Dominguez D, Tournoy J, Hartmann D, Huth T, Crys K, Deforce S, Semeels L, Camacho IE, Marjaux E, Craessaerts K, Roebroek AJ, Schwake M, D'Hooge R, Bach P, Kalinke U, Moechars D, Alzheimer C, Reiss K, Saftig P, Bach P, Kalinke U, Moechars D, Alzheimer C, Reiss K, Saftig P.

Rozzini R, Ferrucci L, Losonczy K, Havlik KA, Lyketsos CG, Breitner JC, Welsh-Bohmer KA. Does NSAID use modify cognitive trajectories in the elderly? The Cache County study. Neurology. 2007; 69: 275–82.

Rogers J, Kirby LC, Hempelmann SR, Berry DL, McGeer PL, Kaszniaik AW, Zalisinski J, Colief M, Mansukhani L, Willson P, Kogan F. Clinical trial of indomethacin in Alzheimer's disease. Neurology. 1993; 43: 1609–11.

Masliah E, Hansen L, Adame A, Crews L, Bard F, Lee C, Seubert P, Games D, Kirby L, Schenk D. Abeta vaccination effects on plaque pathology in the absence of encephalitis in Alzheimer disease. Neurology. 2005; 64: 129–31.

Nicoll JA, Wilkinson D, Holmes C, Steart TA, Van Vickle GD, Kuo YM, Lopez J, Brune D, Ferrer I, Masliah E, Newel AJ, Beach TG, Castano EM, Roher AE. Amyloid-beta peptide remnants in Alzheimer's disease patients: a biochemical analysis. Am J Pathol. 2006; 169: 1048–63.

Patton RL, Kalback WM, Esh CL, Cocchio TA, Van Vickle GD, Luehrs DC, Kuo YM, Lopez J, Brune D, Ferrer I, Masliah E, Newel AJ, Beach TG, Castano EM, Roher AE. Amyloid-beta peptide remnants in Alzheimer's disease patients: a biochemical analysis. Am J Pathol. 2006; 169: 1048–63.

Signorell A, Muller-Tillmanns B, Lemke U, Henke K, Moritz E, Garcia E, Wollmer MA, Umbricht D, de Quervain DJ, Hofmann D, Middledaen A, Papassotiropolous A, Nitsch RM. Antibodies against beta-amyloid slow cognitive decline in Alzheimer's disease. Neuropathology. 2003; 38: 547–54.

Ogrogozo JM, Gilman S, Dartigues JF, Laurent B, Puel M, Kirby LC, Jouanny P, Dubois B, Eiseren L, Filliman S, Michel BF, Boada M, Frank A, Hock C. Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization. Neurology. 2003; 61: 46–54.

Boche D, Nicoll JA. The role of the immune system in clearance of abeta from the brain. Brain Pathol. 2008; 18: 267–78.

Monsonego A, Mitiloma J, Petrovic S, Zota V, Nemirovsky A, Baron R, Fisher Y, Owens T, Weiner HL. Abeta-induced meningoencephalitis is IFN-gamma-dependent and is associated with T cell-dependent clearance of Abeta in a mouse model of Alzheimer's disease. Proc Natl Acad Sci USA. 2006; 103: 5048–53.

Feilert M, Boncristiano S, Bondolfi L, Stalder A, Deller T, Staufenbriel M, Mathews PM, Jucker M. Cerebral hemorrhage after passive anti-Abeta immunotherapy. Science. 2002; 298: 1379.

Bancher C, Braak H, Fischer P, Jellinger KA. Neuropathological staging of Alzheimer lesions and intellectual status in Alzheimer’s and Parkinson’s disease patients. Neurosci Lett. 1993; 162: 179–82.

Geula C, Nagybery N, Nicholas A, Wu CK. Cholinergic neuronal and axonal abnormalities are present early in aging and in Alzheimer disease. J Neuropathol Exp Neurol. 2008; 67: 309–18.

Rub U, Del Tredici K, Schultz C, Thal DR, Braak E, Braak H. The evolution of Alzheimer's disease-related cytoskeletal pathology in the human raphé nuclei. Neuropathol Appl Neurobiol. 2000; 26: 553–67.

Ohm TG, Muller H, Braak H, Bohl J. Close-meshed prevalence rates of different stages as a tool to uncover the rate of Alzheimer's disease-related neurofibrillary changes. Neuroscience. 1995; 64: 299–17.

Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist GT, Holt DP, Bergstrom M, Saviccheva I, Huang GF, Estrada S, Ausen B, Debnath ML, Barletta J Price JC, Sandell J, Logresti BJ, Wall A, Koivisto P, Antoni G, Mathias CA, Langstrom B. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol. 2004; 55: 306–19.

Verheof NP, Wilson AA, Takeshita S, Trop L, Hussey D, Singh K, Kung HF, Kung MP, Houle S. In vivo imaging of Alzheimer disease beta-amyloid with [11C]SB-13 PET. Am J Geriatr Psychiatry. 2004; 12: 584–95.

Shoghi-Jadid K, Small GW, Agdeppa ED, Kepe V, Ercoli LM, Siddarth P, Read S, Satyamurthy N, Petric A, Huang SC, Barrio JR. Localization of neurofibrillary tangles and beta-amyloid plaques in the brain of living patients with Alzheimer disease. Am J Geriatr Psychiatry. 2002; 10: 24–35.

Small GW, Kepe V, Ercoli LM, Siddarth P, Bookheimer SY, Miller KJ, Lavretsly H, Burggren AC, Cole GM, Vinters HV, Thompson PM, Huang SC, Satyamurthy N, Phelps M, Barrio JR. PET of brain amyloid and tau in mild cognitive impairment. N Engl J Med. 2006; 355: 2652–63.
133. Engler H, Forsberg A, Almkvist O, Blomquist G, Larsson E, Savitcheva I, Wall A, Ringheim A, Langstrom B, Nordberg A. Two-year follow-up of amyloid deposition in patients with Alzheimer's disease. Brain. 2006; 129: 2856–66.

134. Ikonomovic MD, Klunk WE, Abrahamson EE, Mathis CA, Price JC, Tosopelas AD, Lopresti BJ, Ziolko S, Bi W, Paljui WR, Debath ML, Hope CE, Isanski BA, Hamilton RL, Dekosky ST. Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. Brain. 2008; 130: 45.

135. Lockhart A, Lamb JR, Ooredkar T, Sue LI, Joyce JN, Ye L, Libri V, Leppert D, Beach TG. PiB is a non-specific imaging marker of amyloid-beta (Abeta) peptide-related cerebral amyloidosis. Brain. 2007; 130: 2670–275.

136. Mathis CA, Wang Y, Holt DP, Huang GF, Debnath ML, Klunk WE. Synthesis and evaluation of 11C-labeled 6-substituted 2-arylbenzothiazolines as amyloid imaging agents. J Med Chem. 2003; 46: 2740–54.

137. Papasotirioupolous A, Fountoulakis M, Dunckley T, Stephan DA, Reiman EM, Rogaev E, Schmeltz EE, Mathis CA, Price JC, Tsopelas ND, Mortilla L, Gusella J, Roses A, Crapper PH. Cloning of a gene bearing missense mutations in a mouse isogenic model of familial Alzheimer's disease. Proc Natl Acad Sci USA. 1992; 2: 330–4.

138. Bertram L, Tanzi RE. The genetic epidemiology of neurodegenerative disease. J Clin Invest. 2005; 115: 1447–59.

139. St George-Hyslop PH, Haines J, Rogaev E, Mortilla M, Vaula G, Pericak-Vance M, Foncin JF, Montesi M, Bruni A, Sorbi S, Rainero I, Pinessi C, Lin C, Holman K, Tsuda T, Rogaev EI, Sherrington R, Rogaeva EA, Levesque G, Ikeda M, Liang Y, Chi H, Lin C, Holman K, Tsuda T, Rogaev EI, Sherrington R, Rogaeva EA, Levesque G, Ikeda M, Liang Y, Chi H, Lin C, Holman K, Tsuda J, Mar L, Sorbi S, Nacmias B, Piacentini S, Amaducci L, Chumakov I, Cohen D, Lannfelt C, Fraser PE, Rommens JM, St George-Hyslop PH. Familial Alzheimer’s disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer’s disease type 3 gene. Nature. 1995; 376: 775–8.

140. Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M, Chi H, Lin C, Holman K, Tsuda T, Mar L, Foncin JF, Bruni AC, Montesi MP, Sorbi S, Rainero I, Pinessi C, Lin C, Holman K, Tsuda T, Farrer L, Cantu J-M, Duara R, Amaducci L, Bergamin L, Gusella J, Roses A, Crapper McLachlan D. Genetic evidence for a novel familial Alzheimer’s disease locus on chromosome 14. Nat Genet. 1992; 2: 330–4.

141. St George-Hyslop PH, Tanzi RE, Polinsky RJ, Haines JL, Neel L, Watkins PC, Myers RH, Feldman RG, Pollen D, Drachman D, Growdon J, Bruni A, Foncin JF, Salmon D, Frommelt P, Amaducci L, Sorbi S, Piacentini S, Stewart GD, Hobbs WJ, Conneally PM, Gusella JF. The genetic defect causing familial Alzheimer’s disease maps on chromosome 21. Science. 1987; 235: 885–90.

142. Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, Giuffra L, Haynes A, Irving N, James L, Mant R, Newton P, Rooke K, Roques P, Talbot C, Pericak-Vance M, Roses A, Williamson R, Rossor M, Owen M, Hardy J. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer’s disease. Nature. 1991; 349: 704–6.

143. Levy-Lahad E, Wasco W, Poorkaj P, Romano DM, Oshima J, Pettinelli WH, Yu CE, Jondro PD, Schmidt SD, Wang K, Crowley AC, Fu Y-H, Guenette SY, Galas D, Nemeck W, Wijsman EM, Bird TD, Schellenberg, GD, Tanzi RE. Candidate gene for the chromosome 1 familial Alzheimer’s disease locus. Science. 1995; 269: 973–7.

144. Rogaev EI, Sherrington R, Rogaeva EA, Levesque G, Ikeda M, Liang Y, Chi H, Lin C, Holman K, Tsuda T, Rogaev EI, Sherrington R, Rogaeva EA, Levesque G, Ikeda M, Liang Y, Chi H, Lin C, Holman K, Tsuda J, Mar L, Sorbi S, Nacmias B, Piacentini S, Amaducci L, Chumakov I, Cohen D, Lannfelt C, Fraser PE, Rommens JM, St George-Hyslop PH. Familial Alzheimer’s disease locus on chromosome 1 in late-onset familial Alzheimer disease. Proc Natl Acad Sci USA. 1993; 90: 9177–81.

149. Zuberen KG, Stiller S, Stabler S, Kopp U, Hughes HB, Cohen BM, Moosy J. Association of the apolipoprotein E epsilon 4 allele with clinical subtypes of autopsy confirmed Alzheimer’s disease. Am J Med Genet. 1994; 54: 199–205.

150. Knopman D. Alzheimer type dementia. In: Dickson D, editor. Neurodegeneration: the molecular pathology of dementia and movement disorders. Basel: ISN Neuropath Press; 2003. pp. 24–39.

151. Ghebremedhin E, Schultz C, Thai DR, Rub U, Otm TG, Braak E, Braak H. Gender and age modify the association between APOE and AD-related neuropathology. Neurology. 2001; 56: 1696–701.

152. Thai DR, Sassini I, Schultz C, Haass C, Braak E, Braak H. Fleecy amyloid deposits in the internal layers of the human entorhinal cortex are comprised of N-terminal truncated fragments of Abeta. J Neuropathol Exp Neurol. 1999; 58: 210–6.

153. Gellermann GP, Byrnes H, Striebinger A, Ultrich K, Mueller H, Hillen H, Barghorn S. A beta-globulomers are formed independently of the fibril pathway. Neurobiol Dis. 2006; 30: 212–20.

154. Yankner BA, Duffy CK, Kirschner DA. Neurotrophic and neurotoxic effects of amyloid beta protein: reversal by tachykinin neuropeptides. Science. 1990; 250: 279–82.

155. Lewis J, Dickson DW, Lin WL, Chisholm L, Corral A, Jones G, Yen SH, Sahara N, Skipper L, Yager D, Eckman C, Hardy J, Hutton M, McGowan E. Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. Science. 2001; 293: 1487–91.

156. Oddo S, Billings L, Kessapak C, Cribs DH, LaFerla FM. Abeta immunotherapy leads to clearance of early, but not late, hyperphosphorylated tau aggregates via the proteasome. Neuron. 2004; 43: 321–32.

157. Golz J, Chen F, van Dorpe J, Nilsh RM. Formation of neurofibrillary tangles in P301L tau transgenic mice induced by Abeta 42 fibrils. Science. 2001; 293: 1491–5.

158. Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Rilitch K, Rossor M, Thal L, Winblad B. Current concepts in mild cognitive impairment. Arch Neurol. 2001; 58: 1985–92.

159. Morris JC, Storandt M, Miller JP, McKeel DW, Price JL, Rubin EH, Berg L. Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol. 2001; 58: 397–405.