

Neuropathology of the Alzheimer's continuum: an update

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Abstract

Alzheimer's disease (AD), the most common form of dementia worldwide, is a mixed proteinopathy (amyloid and tau). Originally defined as a clinicopathological entity, it is a heterogenous, multifactorial disorder, currently referred to as the Alzheimer's continuum. Its cardinal pathological features are extracellular β -amyloid (amyloid plaques) and intraneuronal tau aggregates forming neurofibrillary tangles, which are accompanied by vascular amyloid deposits (cerebral amyloid angiopathy), synapse and neuronal loss, as well as neuroinflammation and reactive astrogliosis. In addition to "typical" AD, various subtypes with characteristic regional patterns of tau pathology have been described that show distinct clinical features, biomarker levels, and patterns of key network destructions responsible for cognitive decline. AD is frequently associated with other age-related changes including Lewy and TDP-43 pathologies, hippocampal sclerosis, argyrophilic grain disease, cerebrovascular lesions, and others. These additional pathologies influence the clinical picture of AD, may accelerate disease progression, and can cause a number of challenges in our understanding of the disease including the threshold of each individual pathology to cause dementia and the possibility of underlying common etiologies. This article provides an up-to-date overview of AD neuropathology, its heterogeneity, and additional pathologies in order to explain the difficulties in the diagnosis and the failure of clinical trials in AD patients.

Keywords: Alzheimer's disease, β -Amyloid, Tau pathology, Oligomers, Amyloid angiopathy, Alzheimer subtypes, Regional vulnerability, Co-pathologies

Abbreviations

AD – Alzheimer's disease, **ADNC** - Alzheimer's disease neuropathological changes, **AP** - amyloid plaque, **APP** - amyloid precursor protein, **A β** - β -amyloid peptide, **A β O** - A β oligomer, **CAA** - cerebral amyloid angiopathy, **CBS** - corticobasal syndrome, **CERAD** - Consortium to Establish a Registry for Alzheimer Disease, **CSF** - cerebrospinal fluid, **CVD** - cerebrovascular disease, **DLB** - dementia with Lewy bodies, **EOAD** - early-onset AD, **FTLD** - frontotem-

poral lobar degeneration, **FTLD-TDP** - frontotemporal lobar degeneration with TDP-43, **GVD** - granulovacuolar degeneration, **HcSp-AD** - hippocampal sparing AD, **hp-tau** - hyperphosphorylated tau protein, **LATE** - limbic-predominant age-related TDP-43 encephalopathy, **LATE-NC** - limbic-predominant age-related TDP-43 encephalopathy neuropathological change, **LC** - locus ceruleus, **LOAD** - late-onset AD, **LP-AD** - limbic-predominant AD, **LPPA** - logopenic primary progressive aphasia, **MA-AD** - minimal-atrophy AD, **MCI** - mild cognitive

impairment, **MTL** - medial temporal lobe, **NFT** - neurofibrillary tangle, **NIA-AA** - National Institute of Aging/Alzheimer's Association, **NP** - neuritic plaque, **NT** - neuropil thread, **PART** - primary age-related tauopathy, **PCA** - posterior cortical atrophy, **PHF** - paired helical filament, **SF** - straight filament, **TDP-43** - 43-kDa TAR DNA binding protein 43.

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia, currently affecting around 50 million people worldwide. It accounts for 60-70% of dementia cases in clinical and autopsy series, but it is often associated with other confounding pathologies in the elderly. Its incidence increases from 2/1,000 at age 65-74 years to 37/1,000 at age 85+ [1], and doubles every five years after age 65, with peaks in the tenth decade and slight decrease afterwards [2, 3]. The point prevalence of AD among individuals aged 60+ is 40.2/1,000 persons, the pooled annual period prevalence is 30.4/1,000, and the incidence rate is 15.8/1,000 person-years [4]. With the disproportional increase of the elderly population, the prevalence of AD will approach around 132 million worldwide and up to 16 million cases in the USA by 2050 [5, 6], AD has become a tremendous public health and socio-economic challenge of the 21st century [5]. As available treatments only target symptoms and neither slow nor reverse the progression of the disease, the development of disease-modifying therapeutic procedures is urgent [7].

AD was originally defined as a clinicopathological entity, characterized by progressive memory deficit, involvement of multiple cognitive domains, and a defining pathological substrate with deposition of amyloid- β peptide (A β) in extracellular plaques and cerebral vasculature (cerebral amyloid angiopathy/CAA), neuritic plaques defined by the presence of microtubule-associated hyperphosphorylated tau protein (hp-tau), intraneuronal aggregations of hp-tau manifesting as neurofibrillary tangles (NFTs) in the cell soma, and neuropil threads (NTs), which occur mainly in dendritic compartments and, to a lesser degree, in the axonal domain. These changes are accompanied by early synaptic loss [8], activated microglia [9], mitochondrial dysfunction causing energy loss [10],

neuroinflammation [11], neurovascular dysfunction [12], disruption of the blood-brain barrier [13], neuronal loss and reactive astrogliosis [14]. AD, a mixed proteinopathy (amyloid, tau, TDP-43, and others), is a heterogenous disorder currently referred to as the Alzheimer's continuum [15] with several pathobiological subtypes and various co-pathologies [16]. The final definite diagnosis of AD rests with *post-mortem* neuropathology despite the advent of more sensitive neuroimaging and the use of reliable biomarkers [17]. Even though the classical morphological features of AD have been known for many years, the recently used more sensitive immunohistochemistry techniques for A β and hp-tau have replaced silver-staining techniques and have not only forwarded the diagnosis of AD but allowed a more scientific evaluation of the disease's pathology.

For the neuropathological diagnosis of AD, the updated National Institute on Aging/Alzheimer's Association (NIA/AA) 'ABC' criteria are used [17]. The morphological changes involving brain regions and neuronal cell types following a stereotypical pattern [18] result from selective cellular and regional vulnerability to pathogenic factors and their progression through functionally integrated regions of the brain [19-23] as well as functional networks that result in progression of AD [24, 25]. However, AD is a heterogenous continuum with a variety of clinically and morphologically defined subtypes, currently referred to as Alzheimer's clinical syndrome [15], which presents major challenges for both diagnosis of AD, monitoring and targeting of disease progression [26].

The new definition of AD as a biologically defined spectrum, using the NIA/AA framework [15], enables recognition and diagnosis of the various subtypes of AD [16]. Research consensus guidelines have been proposed for the *intra vitam* biologically-based categorization termed 'ATN', which uses combinations of *in vivo* biomarkers for A β deposition (A), tau pathology (T), and neurodegeneration (N). They use cerebrospinal fluid (CSF) or plasma biomarkers, PET, and functional and structural MRI. The biomarker profiles and categories of the Alzheimer's spectrum referring to AD neuropathological changes (ADNC) have been summarized recently [27].

2. Pathology of Alzheimer's disease

2.1. Macroscopic features

The AD brain often has decreased weight and at least moderate cortical atrophy most marked in the medial temporal lobes (MTLs) with relative sparing the primary motor, somatosensory and visual cortices and enlargement of the lateral ventricles (*ex vacuo* hydrocephalus). Brain atrophy often involves posterior cortical areas, most notable in precuneus and posterior cingulate gyrus in the preclinical stage of AD [28]. However, none of the macroscopic features are specific to AD, and healthy elderly people often show moderate cortical atrophy especially affecting the frontal lobes, with volume loss of the white matter [29]. Medial temporal atrophy affecting amygdala and hippocampus with enlarged temporal horn is typical of AD (Fig. 1). However, this is also seen in other age-related disorders such as hippocampal sclerosis [30].

2.2. Microscopic features

The definite diagnosis of AD requires microscopic examination of multiple brain regions with semiquantitative assessment of the density of

lesions and their topographical distribution. Extracellular amyloid plaques (APs) and intracellular NFTs that are essential for the neuropathological diagnosis, are associated with tau-positive NTs, dystrophic neurites and neuritic plaques (NPs), CAA, reactive astrocytes and activated microglia, and neuroinflammation are present. These lesions result in loss of synapses and neurons in vulnerable regions leading to brain atrophy and the characteristic clinical picture of the disease. Hirano bodies, granulovacuolar degeneration (GVD), TDP-43 deposits, and other lesions may also be present [31, 32].

2.3. Amyloid deposits

APs are formed by the abnormal extracellular nonvascular accumulation and deposition of A β peptides of varying length including those with 40 or 42 amino acids (A β -40 and A β -42), resulting from the sequential cleavage of the amyloid precursor protein (APP) by the enzymes β - and γ -secretases [33]. APP, from which A β is cleaved by endoproteolytic processing, is a large single transmembrane protein, encoded by the APP gene on chromosome 21 [34, 35]. Proteolytic cleavage of APP develops mainly via two exclusive pathways, the amyloidogenic and the non-amyloidogenic pathway, but other alternative pathways (η -secretases, δ -secretase, etc.) have been described for the physiological processing of APP [36]. The initial cut at the β -site of APP is due to the β -secretase activity enzyme BACE1, a transmembrane enzyme with aspartyl protease activity. Clearance by β -secretase yields a slightly shorter soluble fragment (sAPP β) and a correspondingly longer C-terminal fragment (CTF β) or C99 [37]. APP undergoes constitutive shedding by a protease activity called α -secretase, which appears to be a metalloprotease of the ADAM family. TACE (ADAM17) is one of the α -secretase, but ADAM10 is more important for α -secretase activity and sAPP α production. ADAM10 is the physiologically relevant constitutive of α -secretase in primary neurons [38], as has been demonstrated *in vitro* and *in vivo* [39].

Cleavage of APP by α -secretase releases the soluble ectodomain of APP, called sAPP α , and a membrane-tethered intracellular C-terminal fragment, termed CTF α of C83. The amyloidogenic (or

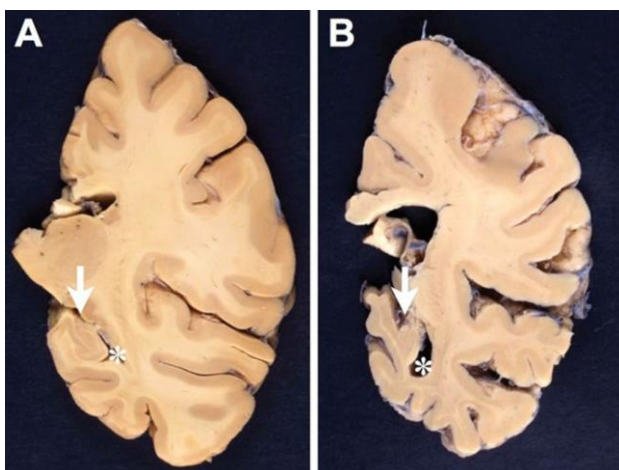


Figure 1. Comparison between formalin-fixed brain slices of the left hemispheres (level of posterior hippocampus) of an aged nondemented individual (A) and an AD patient (B). Note the marked atrophy (thinning of the gyri and deepening of the sulci) in B, in particular hippocampal atrophy (arrow in B) with widening of the inferior horn of the second ventricle (asterisk in B). Photographs by courtesy of Simon Fraser and Arthur Oakley.

β) cleavage of APP is in direct competition with an alternative non-amyloidogenic pathway (cleavage by the α -secretase within the A β sequence) which precludes the formation of amyloidogenic peptides and leads to soluble sAPP α , and has neuroprotective properties preventing A β production [40]. However, aberrant sAPP α production may tilt the cells toward unregulated growth, but the underlying mechanisms are still unknown [41]. Lastly, γ -secretase, a high molecular weight complex that consists of presenilin (PS1, PS2), an aspartyl membrane protease, Aph-1, nicastrin and presenilin enhancer (PEN2), cleaves APP terminal fragments (CTFs) such as C83 and C99, releasing 3 or 4 amino acid peptides from the transmembrane fragment of APP. Notably, γ -secretase is active on APP only following the antecedent α - or β -secretase. The products of γ -secretase cleavage of C83 are a 3-kDA peptide, termed p3 and an APP intracellular domain (AICD), while γ -secretase cleavage of C99 yields the infamous A β peptide and an identical AICD fragment. Besides cleavage by α -, β -, and γ -secretase, other N-terminal fragments (NTFs) of APP have been identified that are generated by unknown proteases [42, 43]. Mounting evidence suggests that astrocytes that have increased levels of APP, β -secretase (BACE1), and γ -secretase play an additional role in AD by secreting significant amounts of A β and contributing to overall A β burden in the brain [44]. BACE1 inhibition more effectively suppresses the initial process of plaque formation, rather than the subsequent phase of plaque growth, which has implications for therapeutic efficiency for the treatment of AD [45]. AD is driven by intraneuronally retained A β produced by the AD-specific β APP-independent pathway [46]. Neuronal A β -42 is enriched in small vesicles at the presynaptic side of synapses [47].

A β deposits contain a mixture of various isoforms. The most common are A β -40 (under physiologic conditions around 90%), A β -38 and A β -42 (less than 10%). A β -40 is produced within the trans-Golgi network (TGN) whilst A β -42 can be made in either the TGN or the endoplasmic reticulum [48]. The specific production of A β -42 in the endoplasmic reticulum of neurons links this compartment with the generation of A β and explains why primarily endoplasmic reticulum localized proteins such as presenilin could induce AD [49]. In-

creased production of A β -42 at the expense of A β -40 is a common feature in both familial and sporadic AD [50]. The latter is believed to be more toxic than A β -40 because of its tendency to aggregate and to form fibrils [51]. The phosphorylation of APP by extracellular-regulated kinase (ERK) and protein kinase C (PKC), in the proteolytic processing of APP has been demonstrated to be critically modulating the generation of A β [52]. The C-terminal APP fragments (APP intracellular domain) are generated by γ -secretase cleavage [53]. γ -Secretase was shown to cleave near the cytoplasmic membrane boundary of APP, called ϵ -site cleavage, as well as in the middle of the membrane domain, called γ -site cleavage, indicating that γ - and ϵ -site cleavage are regulated independently [54]. Ubiquitin-1 has been shown to modulate γ -secretase-mediated ϵ -site cleavage and thus may play a role in regulating γ -secretase cleavage of APP and other proteins [55]. Further cleavage of APP intracellular domain (AICD) fragments by caspase or caspase-like proteases results in additional fragments which, however, does not seem to require antecedent proteolysis of APP [41].

Truncated A β fragments are deposited in APs due to axonal linkage and release of APP [56]. Chemical imaging of evolving AP pathology in a transgenic mouse model for AD suggested initial plaque formation to be seeded by A β -42, followed by plaque maturation upon deposition of A β -40 as well as deposition of others [57]. Due to its higher rate of fibrillization and insolubility, A β -42 is its major component in addition to other A β peptides [58]. A recent report demonstrated the role of HIF-1 α /lncRNA BACE1-AS axis in the transactivator of transcription (Tat)-mediated induction of astrocytic amyloidosis [59]. Advanced biophysical examination of A β derived from AD brain tissue showed polymorphic structures [60]. The terminology of A β plaques is confusing, since a myriad of non-vascular A β deposits have been described, but five major types can be distinguished: (a) primitive or immature plaques are spherical deposits of predominantly A β -42 in the neuropil without a dense core and neurites; (b) diffuse plaques, usually large (50 μ m to several hundred μ m), slightly immunoreactive and ill-limited, contain loose amyloid bundles in the neuropil without degenerating neurites and accompanying microglia (Fig. 2A); (c) stellate

deposits probably related to astrocytes [61]; (d) focal deposits with dense and spherical accumulations of A β -42, surrounded by a neuritic corona containing dystrophic tau-positive neurites and astrocytic components, constituting the “cored”, “classical” or “neuritic” plaques (NPs) (Fig. 2B, 2B1); and finally (e) compact or burnt-out plaques with a dense core of A β -40, absent or tau-negative, ubiquitin-positive neurites. NPs have compact dense amyloid cores composed of more fibrillated forms of A β (Fig. 3). They contain tau-positive dystrophic neurites and are accompanied by synaptic loss, activated microglia and reactive astrocytes [62, 63]. There are differences in the composition of the

aggregates, for example, the A β in NPs has a more varied composition with the presence of A β 40, 42, 43, N-terminus truncated A β and other post-translationally modified forms [64, 65]. Tau-positive NPs begin early in AD, but major tau deposition follows the A β deposition and the clustering of activated microglia [66]. Recent studies unequivocally demonstrated that plaque-associated myeloid cells are derived exclusively from resident microglia [67]. In AD, microglia can eliminate APs through phagocytosis with APOE lipoprotein at an early stage of disease progression [68]. Scanning transmission electron microscopy (STEM) showed three types of fibrillary network structures: amorphous

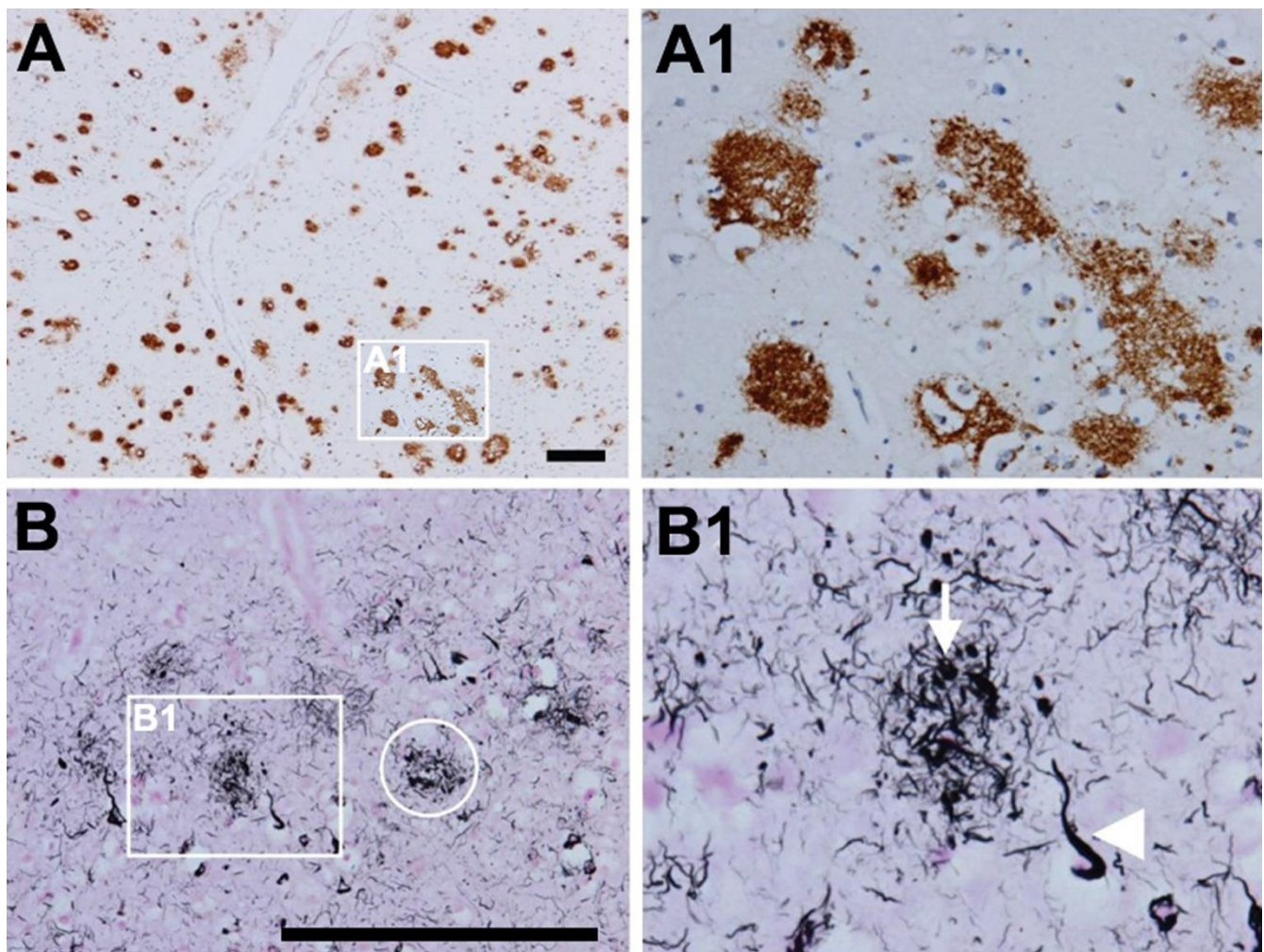


Figure 2. Amyloid and neuritic plaques. A; A1. Multiple diffuse amyloid plaques in the neocortex (antibody 4G8). B, B1. Neuritic plaques that contain A β and tau in distended processes (i.e. dystrophic neurites). Gallyas silver stain visualizes both aggregated A β and tau and is therefore ideal to detect neuritic plaques (ring in B, neuritic plaque; arrow in B1, dystrophic neurite; arrowhead in B1, neurofibrillary tangle). Scale bars: 200 μ m. From [71].

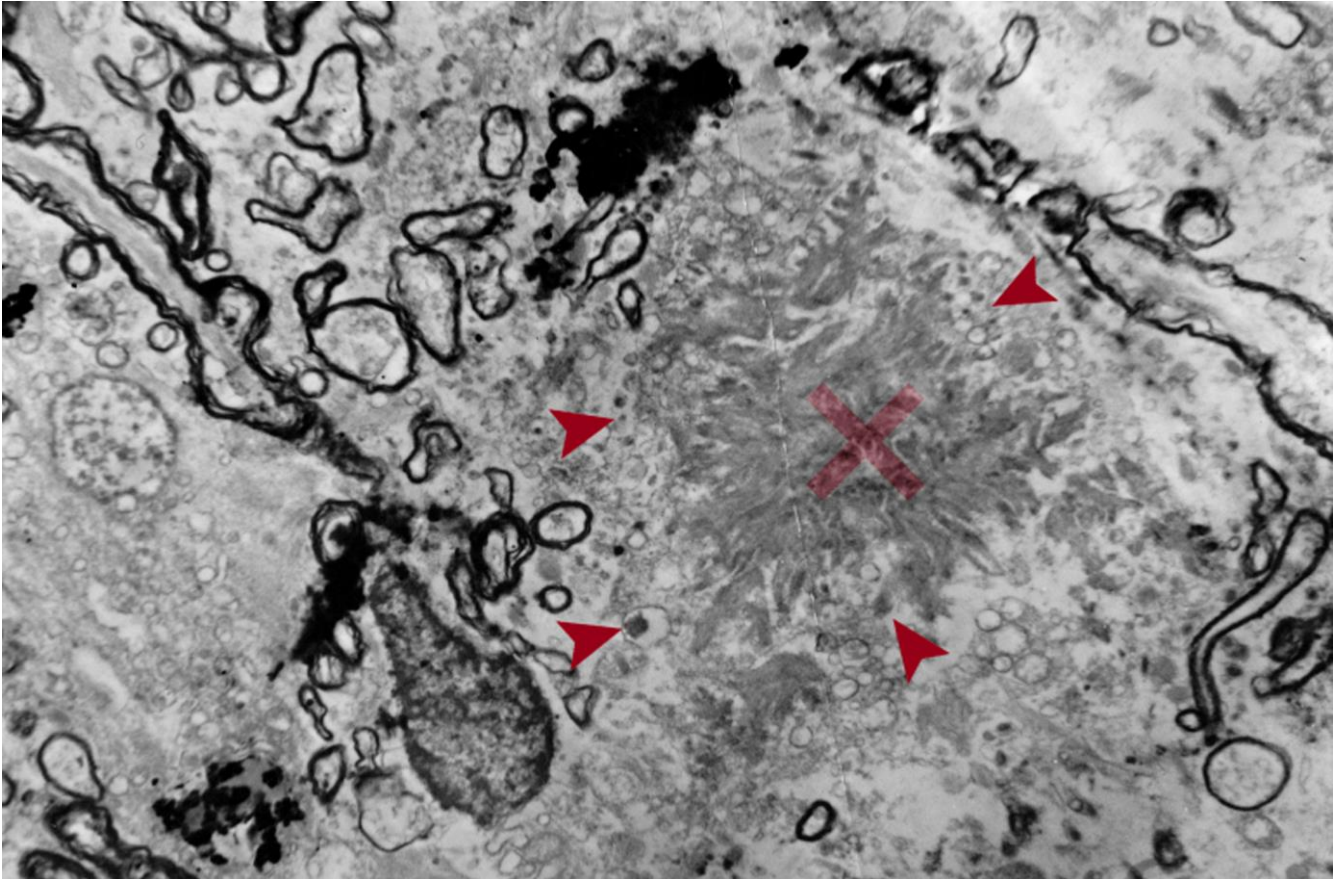


Figure 3. EM image of amyloid core of a neuritic plaque. Radiating bands of amyloid fibrils comprise the core (x). Note the adjacent abnormal fibrils filled with dense bodies (arrows) and surrounding damaged myelin sheaths (x 4000).

network, fibril bundles, and amyloid stars [69]. Although diffuse non-neuritic plaques are generally present before NPs, whether an individual diffuse plaque can actually transfer into an NP or whether these two types develop differently, is not clear at present. A recently described type called the coarse-grained plaque, a relatively large deposit (diameter about 80 μm) characterized by multiple cores and $\text{A}\beta$ -devoid pores, is prominent in the neocortex and associated with homozygous $\text{APO-E}\epsilon 4$ status and CAA. This divergent AP type is similar to CAA, predominantly composed of $\text{A}\beta$ -40, and has been observed particularly in early-onset AD (EOAD) [70].

“Burnt out” plaques are composed of dense cores lacking neuritic components, while the astrocytic processes penetrating the plaque core may represent a regressive stage (“remnant plaques”) [72]. “Cotton wool plaques” are non-compact deposits, made of $\text{A}\beta$ -42 with sparse glial components

and variable neurites but not surrounded by a neuritic corona. They can be detected with H&E staining [61]. $\text{A}\beta$ and tau each begin to aggregate in separate neuroanatomical locations and meet in the cerebral cortex in the NP. This “collision” of both proteins mediated by microglia has devastating consequences in terms of neuronal loss, promoting neurodegeneration and the consequent development of cognitive decline, but this is still under investigation [73].

2.4. Distribution of amyloid deposits

APs in AD brain show a typical distribution with brain areas that are connected via the “default network” typically affected early. In animal models some demonstration of “propagation” along neuronal systems has been observed [74, 75], suggesting some axonal transport of seeds that lead to extracellular deposits.

Most A β deposits are located in the gray matter, while some diffuse or lake-like deposits may be seen in the subpial white matter. Cortical soluble A β protein is a neurotoxic agent [76, 77], and A β oligomers (A β O) may trigger the early phase of the A β seeding process, while depletion of A β O delays the aggregation process leading to a transient reduction of seed-induced A β deposits [78]. The topography of A β deposits depends on the stage of the disease, which led to several staging schemes. Three stages were distinguished: Stage A with amyloid deposits in the basal portions of the frontal, temporal and occipital cortex; in stage B all isocortex is involved, with primary cortices spared and the hippocampus only mildly affected; while stage C shows deposits in the whole isocortex including sensory and motor core fields [18]. Others proposed five amyloid “phases” using sensitive silver staining or A β antibodies: stage 1 or isocortical, stage 2 with additional involvement of hippocampus and entorhinal cortex, stage 3 plus striatum and diencephalic nuclei, stage 4 several brainstem nuclei and medulla oblongata, and stage 5 presenting amyloid deposits in the pons and molecular layer of the cerebellum [79, 80]. These can be reduced to three stages: 1 - isocortical, 2 - allocortical or limbic, and 3 - subcortical. Usually involved is the total isocortex, layers II-V more than layers I and VI [18]. In advanced cases band-like diffuse A β deposits are also seen in the subpial surface of the cortex or in the white matter close to layer VI [71]. Amyloid PET-based staging of A β pathology *in vivo* confirmed its progression in AD [81], and revealed higher plaque counts in entorhinal and occipital regions of typical AD, while other phenotypes showed more severe A β deposition in frontal and parietal cortices [82]. *Post-mortem* analysis of ^{18}F flutemetamol and ^{11}C PiB PET signal showed that it is influenced by both diffuse plaques and cored plaques and, therefore, is likely a function of plaque size and density of A β fibrils in plaques. Brain regions with large volumes of diffuse plaques could yield PET retention levels comparable with lower volume/frequency of cored plaques [83].

2.5. Cerebral amyloid angiopathy

A β peptides also involve the vessel walls, as with CAA, with the more soluble A β -40 as the ma-

ior constituent. 85-90% of confirmed AD cases have some degree of CAA [84]. It mainly accumulates in the interstitium between the smooth cells of the tunica media. Small arteries, arterioles and even capillaries in the cerebral cortex and leptomeningeal vessels are affected [85]. Stage 1: vessels are affected in the isocortex, stage 2: involvement of allocortex, and stage 3: basal ganglia, thalamus, pons and medulla oblongata [86]. Others distinguished four patterns [87]: Type 1: APs with or without CAA in the leptomeninges alone; type 2: CAA in both leptomeningeal and deeper penetrating arteries (Fig 1A); type 3: CAA affects both precapillaries and arterioles; type 4 shows A β deposition in and around blood vessels. Genetically, type 3 (capillary subtype) is more strongly associated with the APOE ϵ 4 allele [87, 88]. Two other types were distinguished: Type 1 affecting capillaries, arterioles and small arteries is associated with APOE ϵ 4, whereas type 2 not involving capillaries is more likely associated with APOE ϵ 2, its most frequent form [89]. Both severe CAA and AD are associated with APOE ϵ 4-positive patients [88]. A more recent staging system is based on the severity of CAA in a single vessel: grade 0: absence of staining, grade 1: a congophilic ring around the otherwise normal-appearing vessel, grade 2: complete replacement of the tunica media by congophilic material, grade 3: involving >50% of vessel circumference, giving a “double-barrel” appearance, and grade 4 or fibrinoid necrosis of the vessel wall with additional amyloid deposits in the surrounding neuropil (“dyshoric changes”) [88]. The parietal and occipital cortices are more vulnerable than the frontal and temporal lobe, and the leptomeningeal vessels more than the parenchymal ones [84]. A β deposition shrinks the cerebral blood vessels by about 8% and reduces the energy supply resulting from decrease of blood flow [90]. CAA can cause small infarcts in the cerebral cortex, while severe CAA may lead to lobar hemorrhages in the frontal and occipital lobes and to diffuse white matter lesions (Fig. 4) [91]. Brain hemorrhage does not appear to be directly linked to amyloid burden in patients with CAA-related intracerebral hemorrhage, because amyloid burden was similarly distributed across the brain hemispheres and no interhemispheric difference was observed for A β burden nor for MRI markers of small vessel disease [92]. CAA and deep perforating arteriopathy are

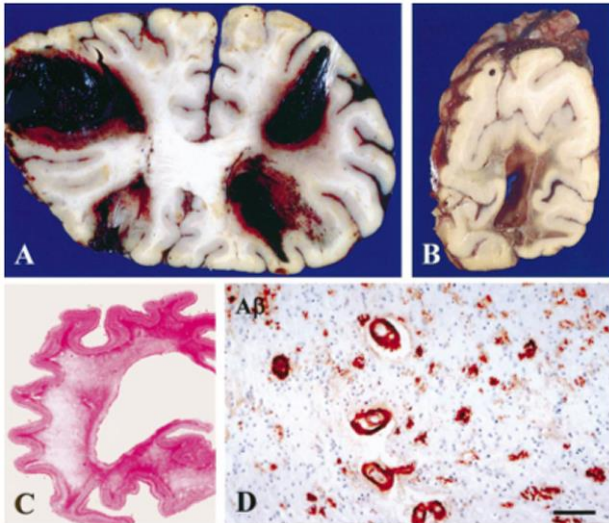


Figure 4. Multiple large hemorrhages in both frontal lobes (A) and occipital lobe (B). Diffuse white matter destruction (C). CAA in many vessels in the cerebral white matter; scale bar 70 μ m (D). From [97].

similar and interact with blood-brain barrier breakdown, endothelial damage, and impaired perivascular A β drainage. Both may cause ischemic lesions and intracerebral hemorrhages [93]. Chronic treatment of a mouse model of AD with fungicides produced A β fibril formation and impairment of A β clearance through neprilysin, suggesting that fungicide residues could be a risk factor for AD via CAA [94]. Although several pathogenic mechanisms, including the disbalance between production and clearance of A β creating a self-reinforcing cycle of increased vascular A β and further CAA and AD progression, have been shown, they do not explain completely the disease pathogenesis [95]. The intersection between CAA and AD points to a crucial role for improving vascular function in the treatment of AD [96].

2.6. Tau pathology

Tau protein is encoded by the MAPT (microtubule-associated protein tau) gene on chromosome 17 [98], which generates a total of 6 isoforms through alternative splicing of exons 2, 3 and 10 in the CNS [99]. Tau protein, the main constituent of NFTs, is involved in the stabilization of neurotubules that leads to the appropriate function of the neuron. Its microtubule-binding regions are made of 3 or 4 repeats (3R or 4R tau), their second repeat (exon 10) being spliced in some isoforms. Com-

bined phosphorylation of Ser202, Thr205, and Ser208 forms a unique post-translational modification configuration that promotes tau aggregation, accelerating the formation of tau filaments and eventually resulting in NFT formation. Tau adopts different stable conformations, consistent with the notion of 'strains' as may be seen with the concept of phenotypic diversity or with different environmental stimuli [100, 101].

Truncation of tau by caspases-3 or -4 is an early event in the development of NFTs [102]. The molecular mechanisms leading to the accumulation of tau are characterized by numerous translational modifications that change its conformation and structural state. Recent studies indicate that the dysregulation and dislocation of splicing factor proline and glutamine rich (SFPQ), the subsequent DNA anomalies and aberrant dynamics of TIA-1-positive stress granules in association with pathological tau may represent a critical pathway which contributes to the rapid progression of AD [103]. Abberant phosphorylation and truncation make tau protein into a pathological entity; paired helical filaments (PHF), the major structural constituents of NFTs, exhibit a greater degree of phosphorylation than normal tau [104]. Tau monomers can aggregate to form oligomers and higher-order fibrils. Whilst A β can largely self assemble, tau phosphorylation is believed to be important for its aggregation [105]. Phosphorylation of Ser208 likely occurs at different disease stages from phosphorylation of Ser202 and Thr205. hp-Tau accumulation causes synaptic impairment, neuronal dysfunction, and formation of NFTs. Tau with site-specific posttranslational modification/soluble hp-tau species impact mitochondria and facilitate neurodegeneration [106]. Recent studies support the hypothesis that tau phosphorylation at Ser208 strongly contributes to unique types of tau aggregates, and may be a reliable marker for the presence of mature NFTs [107].

In AD, tau protein usually accumulates in the somato-dendritic and, to a lesser degree, in the axonal domains of the neuron. NFTs and pretangles are due to accumulation in the soma; NTs occur in dendrites, and the neuritic corona of core plaques is constituted by axonal processes filled by tau proteins (Fig. 2). As major constituents of NFTs and

NTs, they are hyperphosphorylated and aberrantly misfolded, have lost their microtubule stabilizing functions, and contribute to axonal transport deficits [105]. PHFs in AD contain all 6 isoforms of tau protein including those with 3 and 4 repeats (3R- and 4R-tau) in the microtubule binding domain, forming the core of PHF [108]. The tau isoforms show a chronological shift: initially, early pretangles are positive only for 4R, gradually 3R is involved in mature tangles, and finally 4R is replaced by 3R in ghost tangles [109]. Ultrastructurally, NFTs appear as PHFs, i.e., fibrils of ca. 28 nm in diameter that form pairs with a helical tridimensional conformation and a regular periodicity of 65-80 nm [110] or as helical or twisted ribbons [111]. Straight filaments (SFs) show a longer crossover distance and modulations in width from 10 to 15 nm. Both lesions are different from those seen in other tauopathies [112]. PHFs and SFs differ in their interprotofilament packing, and are ultrastructurally polymorph [113]. Visible with cryo-EM, PHFs and SFs are made of two C-shaped protofilaments with a combined cross- β - β -helix structure, without variations in the filamentous structures between sporadic and inherited AD [114]. NTs have an ultrastructure and immunohistochemistry similar to NFTs. Why, despite its axonal origin, PHF tau accumulates primarily in the neuronal cell body and dendrites, is unknown. It shows in three stages: (a)

Pre-NFTs composed of diffuse, or punctuate tau staining occur within the cytoplasm of otherwise normal-looking neurons with well-preserved neurites; or (b) mature intraneuronal NFTs consist of cytoplasmic filamentous aggregates of tau displacing the nucleus toward the periphery of the soma and extending to the proximal segment of the axon. They appear as “flame-shaped tangles” in pyramidal neurons of the hippocampus (Fig. 5) and layer V of association cortices and as “globose tangles” in subcortical nuclei; (c) extraneuronal “ghost” NFTs in dead neurons, showing loss of their nucleus and of stainable cytoplasm [115]. Total loss of functional microglia in advanced late-onset AD (LOAD) promotes widespread intraneuronal neurofibrillary degeneration leading to brain failure [116]. Neuronal tau pathology has been linked to neuronal death and cognitive decline in AD [117], while others suggested that neuronal cell loss is associated with dementia and not the presence of plaques and tangles [118]. It is generally thought that NFTs impede neuronal functioning, but recent data indicate that they can be found in functionally intact neurons integrated in cortical circuits [119-121]. How hp-tau specifically mediates its toxic effects is still unknown, but oligomeric tau species, analogues to A β Os, are potential toxic species besides NFT tau. Recent proteomic studies have identified specific proteins that interact with hp-tau,

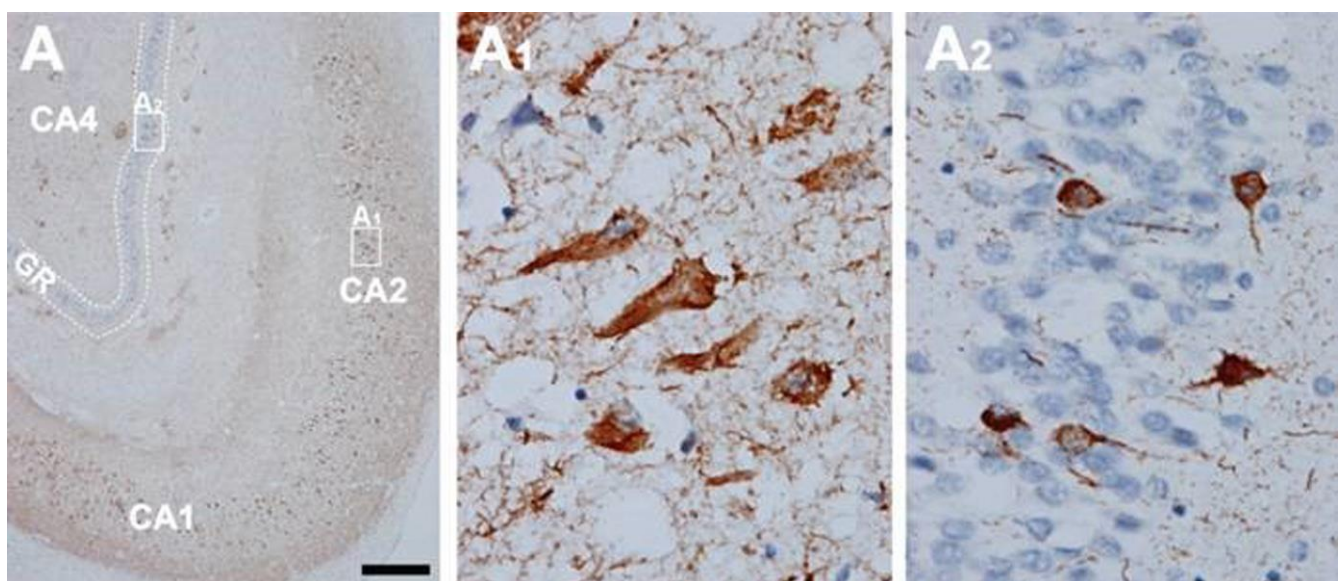


Figure 5. In AD, high amounts of neurofibrillary tangles and neuropil threads are seen in the hippocampus (A). CA1, CA2, and CA4 hippocampal cornu ammonis (Ammon's horn) sectors 1, 2, and 3, respectively; GR, granule cell layer of the dentate gyrus. Immunohistochemistry with antibody AT8. Scale bar: 50 μ m. From [71].

showing novel potential pathogenic mechanisms that are relevant in AD and providing insight into how hp-tau mediates its toxicity in AD [122].

2.7. Topography and spreading pattern of tau

The extent of tau pathology (NFTs and NTs) follows a predictable spatiotemporal progression through functionally integrated brain regions [18], which had been interpreted as a cell-to-cell spreading through prion-like propagation [123-127] or a transneuronal spread through functional networks, associated with a trigger, possibly A β and/or neuronal network activity that could lead to progression of NFT pathology [128]. Since tau is expressed predominantly in neurons rather than glial cells, the detection of tau aggregates in astrocytes and oligodendroglia has given support to the concept that the release of misfolded tau from neurons (or oligodendroglia) may result in uptake into other cells [129]. Microglia could potentially play a role in spreading of tau pathology [130]. Transcellular progression of tau seeds has been observed in early Braak stage in regions predicted to be free of hp-tau [131]. According to the original staging [18], the first NFTs consistently occur in the transentorhinal (perirhinal) region (stage I) along with the entorhinal cortex, followed by the CA1 region of the hippocampus (stage II), indicating a preclinical phase of AD which can last up to 20 years. Limbic structures, such as the subiculum of the hippocampal formation are affected next (stage III), followed by the amygdala, thalamus, and claustrum (stage IV). Stages III and IV are often correlated clinically with mild cognitive impairment (MCI). In stage V, NFTs spread to isocortical areas with the association areas being affected prior and more severely, followed in stage VI by the primary sensory, motor and visual areas, which is usually associated with overt dementia (Fig. 6). This NFT staging has been widely accepted in routine pathology and appears well correlated with the clinical status, at least in the amnesic AD. Imaging *in vivo* tau pathology with tau-specific PET tracers identified NFT pathology reflecting Braak stages IV or higher. It rendered it possible to study the temporal progression of tau pathology *in vivo*, and, therefore, can be used as a reliable biomarker of tau pathology [132-137]. There is an inverse correlation between the accumulation of NFTs and cognitive status; the spread

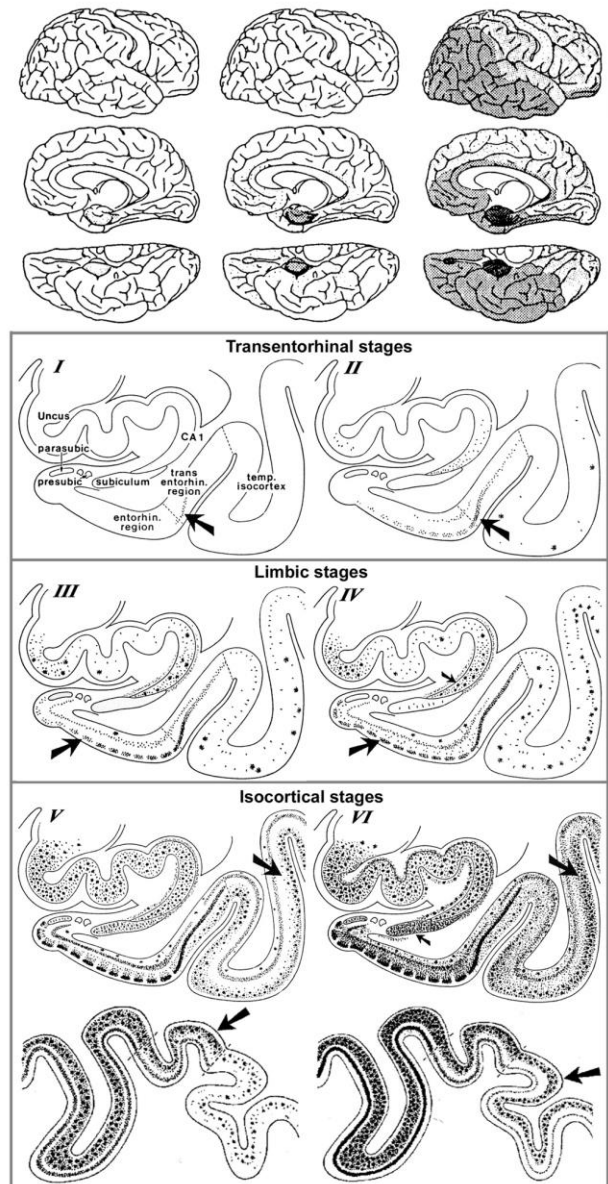


Figure 6. Spreading pattern of neuritic AD pathology. Modified from [18].

and level of tau accumulation reflects the severity of dementia with time [61, 138-140]. The seeding activity is suggested to begin in the transentorhinal/entorhinal regions and anticipates hp-tau pathology in AD, whereas the locus ceruleus (LC) showed seeding only in later NFT stages [141]. However, immunohistochemistry has detected pre-tangle material in multiple subcortical regions, especially in locus ceruleus (LC) neurons [142-144]. Involvement of the subcortical nuclei, not considered in the original Braak scheme, however, occurs in early stages of the disease and has important clinical consequences. The cholinergic nucleus ba-

salis of Meynert and axons of the adrenergic LC projecting neurons are affected already in Braak stages 0/I, associated with severe neuronal loss, while moderate to severe deposition of tau in the LC was only seen in Braak stages above IV [142]. The intralaminar nuclei of the thalamus, the pontine parabrachial region, the medullary reticular formation, the dorsal raphe nucleus, the oculomotor system, and the autonomous nuclei are also affected early and increase with disease progression [142, 145-147]. Nigral pathology including hp-tau (NFTs) accumulation and α -synuclein aggregates is common in elderly patients with and without AD, and may be related with extrapyramidal symptoms [148-150].

2.8. A β and tau pathology - chicken or egg?

The causes of sporadic AD are far from being understood, while the hallmarks that distinguish AD from other neurodegenerative diseases – namely A β plaques and NFTs - have been known for many years. The physiological and pathological roles of tau and A β , and their implications for AD pathology and therapeutics have been reviewed recently [151]. Many studies have linked A β and tau and raised the possibility that protein-protein interactions are the key for both spreading and toxicity of these two abnormal proteins [152]. Several models of interaction have been suggested: (1) The seeding of toxic tau is enhanced by the presence of A β ; (2) the toxicity of A β depends of the presence of tau; (3) A β and tau enhance each other's toxicity. Modern network-based models revealed ways in which A β and tau protein might interact with each other to enhance the propagation of AD, thus shedding light on the importance of protein clearance and protein interaction mechanisms in the development of AD pathology [153, 154] [155]. Soluble oligomeric A β is hypothesized to be a possible cause of the hyperphosphorylation of tau and the development of NFTs. The presence of APs accelerates both the formation of hp-tau aggregates [156] and its interneuronal transfer [157]. The A β O hypothesis was introduced in 1998, suggesting that the brain damage leading to AD was initiated by soluble ligand-like A β O [158]. The extension of tau pathology is different from the spread of A β deposition that is related to diffusion of soluble A β in the extracellular space [159, 160].

Quantification of ADNC in formalin-fixed *post-mortem* human brain tissue detected high amounts of A β in the frontal cortex and striatum, and of hp-tau in the frontal cortex and hippocampus of cases with high ADNC pathology load [161]. The most recent version of the amyloid cascade hypothesis assumes AD arises from synaptic toxicity mediated by soluble A β O, leading to synaptic dysfunction and loss. Age-related aggregation of A β and its apparent downstream effects on microglia, astrocytes, and neurons, including the post-translational modification of the tau protein, seems necessary for AD symptom expression [162]. While an optimal concentration of A β is thought to likely maintain synapses, alterations in the proteolytic processing of APP may cause dyshomeostasis of A β , increasing the levels of A β -42, and initiating AD by setting off a chain of events that leads to the accumulation of tau and downstream neuronal cell death [163]. Soluble A β O are now suggested to cause neuronal damage [76]. They are believed to insert into membranes, while others support ligand-like accumulation at particular synapses, providing a substantial molecular basis for the cause of AD [164]. Recent data support the hypothesis that A β enhances tau pathology through increased spreading of tau induced by PHF *in vivo* [165-168], and that A β O promote tau seeding potentiating intracellular tau aggregation [169, 170]. Intraneuronal A β accumulation is suggested to precede tau pathology in the entorhinal cortex [171] and to interact with hippocampal and cortical tau pathology, while in the absence of A β tau deposition may be insufficient for the neurodegeneration process that leads to AD [172]. Many data supporting a toxic role for A β O have backed the A β O hypothesis for AD pathogenesis, but further advances in A β O structure-function studies are needed [158]. Recent studies point to a role for exosomes in the spreading of toxic A β O and the associated disease progression in the AD brain [173]. However, the traditional consensus of the amyloid paradigm as a singular cause of AD has been under revision, with the accumulation of new pathological evidence [174]. New theories suggest that various mechanisms, including prion-like spread of A β and tau, vasoconstrictions, growth hormone secretagogue receptor 1 α (GHSR1 α), and neuroinflammation, come together at a crossroad that ultimately leads to AD [11], while others suggested that extracellu-

lar A β and tau act in parallel and upstream of APP [175, 176]. However, recent findings have shown that the soluble form of APP binds directly to GABA_ABR1a and modulates synaptic transmission [177], while that of A β aggregates do not need APP overexpression [178] but are performed by extracellular exosomes [173]. A β O_s are deposited inside synaptic terminals [179], enriched in small vesicles at the presynaptic side [47], and enhance synaptic dysfunction in AD [180]. According to others, A β and hp-tau may develop concomitantly within synaptic terminals [181, 182] and cause abnormalities at synapses [183]. On the other hand, preclinical evidence indicates that tau pathology can progress independently of A β accumulation and arises downstream of genetic risk factors for AD by an aberrant metabolic pathway [184]. The argument that insoluble A β and tau deposits begin forming concomitantly in the cerebral cortex of AD brains would be consistent with the argument in favor of the pathogenic importance of tau deposition. Recent quantitative studies did not find regional association between A β -42 and insoluble tau, but a higher regional association between total A β -42 and soluble tau phosphorylation. This provides evidence supporting the local interplay between A β and soluble hp-tau in AD brains [185], and accumulating evidence suggests that both pathologies have synergistic effects. The complex A β -tau interaction is important for elucidating disease pathogenesis and the design of next-generation AD therapeutical trials [153]. Targeting the common epitope could be a more effective treatment strategy than targeting only A β or tau alone [186].

Mounting data suggest that the prion-like spreading of diffusible oligomers and other protein aggregates from cell to cell within the brain, probably through specific neuronal networks, may contribute to AD progression [128, 187]. APP overexpression is not a prerequisite for the prion-like induction of cerebral A β deposition that may contribute to disease progression in AD [178], and the multiple failures of previous anti-A β drugs may suggest that in the AD brain, the accumulation of A β could be secondary to an unknown 'initial disrupting event' [188]. Processing and clearance of A β and tau could be related to a bidirectional relationship between ADNC and autophagy [189]. Seeded templating and neurotoxicity are two of the

most critical properties attributed to oligomers that have been documented for misfolded proteins in neurodegeneration [190]. It has been speculated that cellular prion protein (PrP^C) is a critical player in the interplay between A β and tau propagation in a large group of AD cases. Pre-existing hp-tau pathology interacting with PrP^C appears to be a prerequisite for A β function as a hp-tau pathology acceleration via PrP^C [165]. Toxic tau oligomers (tauO_s) and toxic oligomeric A β assemblies (AO_s) have prionoid characteristics and are responsible for cell-to-cell spreading in the brain. Both extra- and intracellular A β O_s and tauO_s (not NFTs and APs) may represent novel targets of AD research and therapeutic trials [191]. Preventing soluble A β O formation and targeting their N-terminal residues with antibodies could be an attractive combined therapeutic approach [178].

Recent studies found striking patient-to-patient heterogeneity in the hyperphosphorylated species of soluble oligomeric seed-competent tau. Its seeding capacity correlates with the aggressiveness of the clinical disease, and some post-translational modification sites appeared to be associated with both seeding activity and worse clinical outcomes, suggesting that different individuals with "typical" AD have distinct biochemical features of tau that correlated with differences in the aggressiveness of clinical course [192], supporting an important causal role of tau as a driver of clinical dysfunction in AD [193]. The synergism between A β deposition, NFT neurodegeneration, and CAA may be a better predictor of cognitive decline or disease progression than either pathology alone [194] (Fig. 7).

2.9. Synaptic and neuronal loss

Essential neuropathological features of AD are loss of synapses and selected neuronal cells (20-40% in neocortex and 25-65% in hippocampus) as the main pathological substrate of cortical atrophy. Its regional and laminar pattern parallels the distribution of NFTs and has been suggested to be a better correlate of cognitive deficits than the A β burden [139, 196]. Little is known about the molecular basis of selective neuronal vulnerability in AD and the molecular pathways that lead to

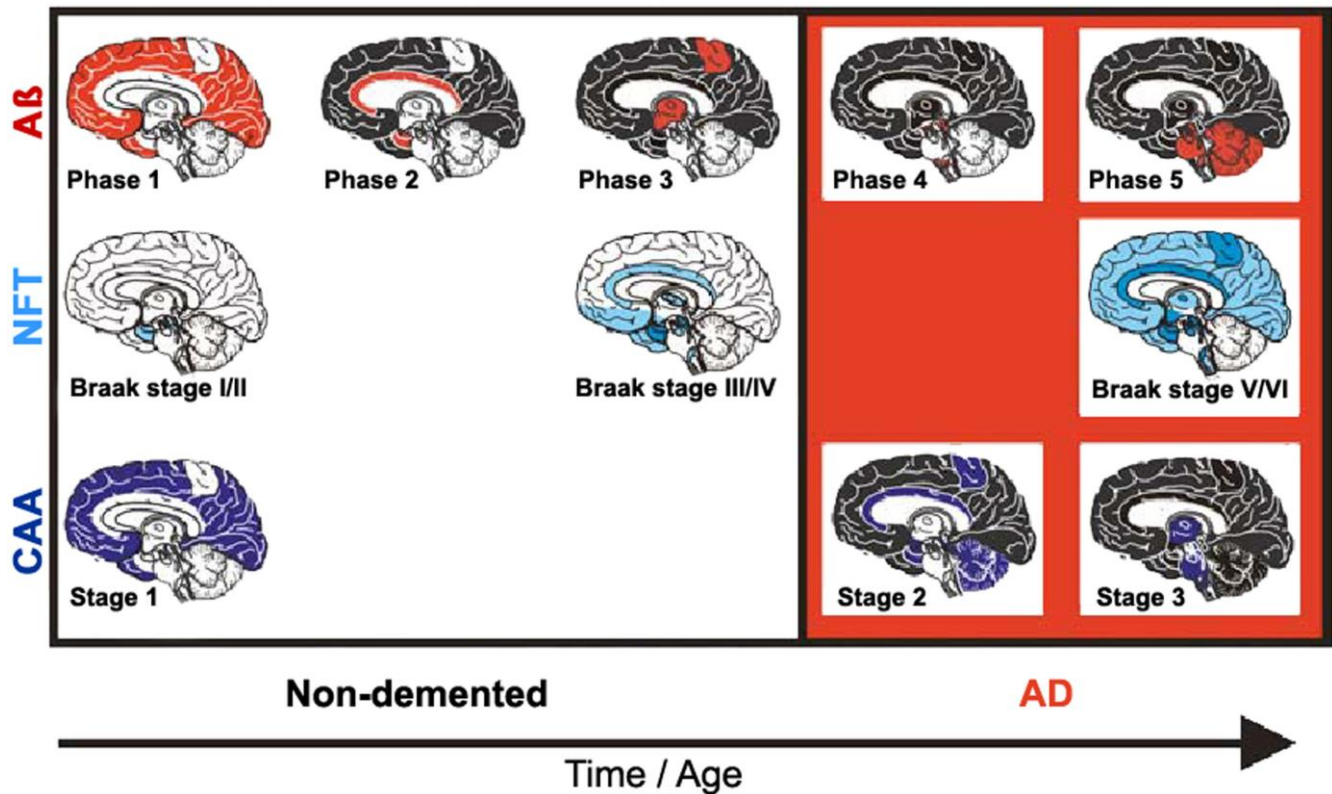


Figure 7. Staging of A β , NFT, and CAA in non-demented (pre-AD) and demented AD patients. From [195].

neurodegeneration, a key characteristic of the disease. It is the result of multiple molecular changes of interacting genes and pathways within vulnerable neurons [25]. The relationship between cellular senescence in the context of aging and AD have been reviewed recently [197]. Age-related intraneuronal aggregation of A β is colocalized with mitochondria and endosomes and less so with lysosomes and autophagosomes. Understanding age-related changes in intraneuronal A β may lead to application of countermeasures to prolong dementia-free health span [198]. The intraneuronal accumulation of A β may involve synaptic dysfunction and the formation of APs in AD; intraneuronal A β -42 has been reported to disrupt the normal cytoarchitecture of neurites. Recent studies indicate that in AD, vulnerable-neuron-specific dysregulation of polypyrimidine tract binding protein (PTB) (NCBI gene ID 5725), a regulator of alternative splicing [199], is the protein most highly correlated to tau in the principal neurons of the entorhinal cortex layer II (EC II). PTB could precipitate a 3R/4R tau imbalance in these neurons and explain the premature accumulation of NFTs, thus explaining the vulnera-

bility of EC II neurons [25]. The neurotoxic effect of astrocyte-derived exosomes (ADE) is evident with the overlap of AP density and C3/4 fragments (complement factors) observed in early AD [200]. Although tangle-bearing neurons can be long lasting in regions where NFTs occur at a presymptomatic stage, neuronal loss occurs early in the course of the symptomatic disease [201]. Two mechanisms of neuronal death in AD have been discussed: one affecting tangle-bearing neurons that will lead to ghost extracellular tangles, another affecting tangle-free neurons, at least in part by apoptosis [202-204]. Inflammation-induced hyperphosphorylation of tau destabilizes the microtubule-actin network and impairs axonal transport and disturbs energy metabolism in the axon, inducing further tau phosphorylation. Accumulating data point to the fact that this facilitates the formation of PHFs, further impairs axonal transport leading to complete blockage and axonal leakage, and induces loss of synaptic contacts promoting activation of microglia and reactive astrogliosis [56]. Microglia have been shown to instigate tau pathology in diverse ways, inducing tau aggregation by proin-

flammatory cytokine release [205, 206], and spreading hp-tau oligomers or NFTs through exosome secretion [130].

Synaptic loss that is possibly driven by A β and tau pathology has been suggested to precede neuronal loss [207]. Synapses are present in APs and their total number decreases with time [61, 208]. Their loss has been demonstrated ultrastructurally and immunohistochemically [209]. In late stages of AD synapse loss ranges from 10 to 60%, most severely in the frontal and mesiotemporal regions. Synapse loss by activated astrocytes producing different secretomes reduce protein synthesis for synapse formation, resulting in synaptic loss found in AD [210]. There is a close relationship between A β accumulation and synaptic loss that may provide direction for the development of potential disease-modifying treatments of AD [211]. EOAD is associated with a higher burden of ADNC and a higher rate of neocortical atrophy and synapse loss than the much more common and apparently sporadic LOAD [212]. However, synaptic loss is not a unique hallmark of AD and occurs in many other brain diseases [213].

2.10. Neuroinflammation

Activated microglia operating as phagocytes are frequently observed around A β plaques driving an inflammatory response, which can be activated by multiple factors in the local environment [214], in particular by the presence of A β in the cortex, indicating a “toxic” response which corrupts neurons as collateral damage (“bystander effect”) [215]. Tau-positive NPs being early in AD, however, major tau deposition follows the accumulation of A β and clustering of activated microglia. An increase in membrane attack complex formation leads to increased tau pathology and neuronal loss [216]. On the other hand, microglia may contribute to elimination of tau deposits by phagocytosis [217, 218]. Different states of microglia activation, corresponding to regional activation of A β and tau, are present simultaneously in the same brain. The clustering of activated microglia is greatest in the primary motor cortex, a region relatively spared compared to the severely affected inferior temporal cortex in AD. This suggests that microglial activation is not prominent in the early phase of AD

pathophysiology [66]. Recent studies in hp-tau mice demonstrated that microglia are not the agitators of tau aggregation, but different results about the involvement of microglia in tau aggregation and clearance were presented [219, 220]. Thus, the functional role of microglial activation with hp-tau oligomers still remains elusive. Gene-profiling technologies applied to isolated microglia have challenged the hypothesis that there is one acute-type (microglial drivers) of inflammation in the human brain causing accelerated proinflammatory damage in AD. These studies have shown that many of the microglia genes expressed in increased levels reflect a response to restore homeostasis and limit inflammatory damage [221]. On the other hand, there is an early microglia reaction to AD pathology, but a loss of healthy microglia is the prominent feature in severely affected regions of the AD brain [222]. In addition, there is a non-disease-specific response of microglia to neuronal damage, with upregulation of phagocytotic activity to remove damaged neurons and synapses by CD68 immunoreactivity of lysosomes [73]. Their numbers increase on promotion to neuronal damage associated with NFTs [62], which is due to enhanced production of inflammatory cytokines, such as IL-21 and increase in T follicular helper cells. The strong immune response is insufficient at clearing up A β and instead exacerbates inflammation [223]. Reactive astrocytes that may react to cytokines and other agents produced by pro-inflammatory microglia, are observed around APs, though less frequently compared to microglia. Reactive astroglia burden occurs later in AD and correlates mainly with tau pathology [31].

2.11. Pathology of preclinical AD

Amyloid and neuritic plaques and NFTs occurring in non-demented elderly individuals, represent asymptomatic or preclinical AD (pre-AD), while clinical AD affects subjects with late stages of ADNC. Both AD and pre-AD cases often exhibit CAA, which is also observed in non-AD cases, i.e., those without ADNC. Patients with MCI do not always have ADNC even though they have a risk of developing dementia in 10-12% and sometimes do not have any discernable pathology [224, 225]. The presence of NFTs and CAA in cases without APs,

Table 1. Showing the translation of the Thal, Braak/BNE stages and CERAD plaque score into A, B, C for assessment of the level of AD neuropathological change. From [174], modified after [17].

A- Aβ Plaque Score (Thal)	B- Braak/Modified Braak Stage (Braak and Braak)	C- Neuritic plaque Score (CERAD)
A0- No A β plaques	B0- No tangles or threads	C0-No neuritic plaques
A1-Thal phase 1 or 2	B1-Braak stage I or II	C1-CERAD score sparse
A2-Thal phase 3	B2-Braak stage III or IV	C2-CERAD score moderate
A3-Thal phase 4 or 5	B3-Braak stage V or VI	C3-CERAD score frequent

classified as non-AD, suggests that they may precede AP pathology or may present a pre-amyloid plaque stage not yet included in the current criteria for the neuropathological diagnosis of AD [226]. Increased soluble/dispersible A β in pre-AD compared to fully developed suggests that, in addition to more severe and widespread ADNC, soluble A β aggregates play a role in the conversion of pre-AD to clinical AD [31]. Cognitively impaired individuals presenting with an early onset AD phenotype showed higher rates of tau PET accumulation, while among cognitively unimpaired individuals higher rates of tau accumulation were associated with faster rates of memory decline [227].

2.12. Neuropathological diagnosis of Alzheimer's disease

Histopathological examination of the brain has to establish that ADNC are present in sufficient densities and extensions to distinguish AD from other age-related disorders [61]. Because the disease affects the whole brain, it is not sufficient to make the diagnosis of AD just on one or two brain blocks; instead, multiple brain areas have to be examined and a staging protocol has to be established. The current algorithms for the pathological diagnosis of AD are based on semiquantitative assessment of APs and NFTs providing reasonable interrater agreement when using standardized criteria [228]. Current guidelines include (a) cut-off quantitative values for APs and tangles [17, 229]; (b) the semiquantitative assessment and age-adjustment of NPs in the Consortium to Establish a

Registry for Alzheimer's Disease (CERAD) protocol [230]; (c) topographic staging of neuritic/tau pathology [18], re-evaluated by immunohistochemistry [231]; and (d) the progress and distribution of A β phases [79]. In order to develop a system that combines all the above pathological features, the NIA/AA established a composite score comprising the extent of involvement/spread of cerebral A β based on the progression model by the Thal phases: (A), that of NFTs based on the progression model of Braak, (B), and the CERAD score, which describes the density of neuritic amyloid plaques based on certain key locations in the neocortex, (C) (Table 1). From this combination, it gave a likelihood for the degree of AD neuropathological changes in an individual case. Sufficient agreement in AD diagnosis could be reached only when the lesions are considerable (Braak NFT stage V and VI) with 91% agreement, while for mild lesions it was poorer (for Braak stage I and II, agreement was only around 50%) [228, 232, 233].

Combined Braak and CERAD scores in the NIA-RI (National Institute on Aging and Reagan Institute) criteria that apply only to demented persons, relate dementia to ADNC with high, intermediate and low likelihood [234]. They have been widely used in Anglo-American neuropathology and are now replaced by the NIA/AA guidelines. Although the sensitivity and specificity of the NIA-RI criteria has been proposed to be around 90%, only 30 to 57% of the brains of patients with the clinical diagnosis of probable AD showed "pure" ADNC, thus reducing their predictive value to 38% [235].

Table 2. ABC criteria for the diagnosis of Alzheimer's disease-related pathology. Modified from [17].

Thal phase for Aβ plaques	Level of AD neuropathologic change				CERAD	
	A	B				C
		0 or 1	2	3		
0	0	Not	Not	Not	0	neg
1 or 2	1	Low	Low	Low	0 or 1	neg or A
1 or 2	1	Low	Intermediate	Intermediate	2 or 3	B or C
3	2	Low	Intermediate	Intermediate	any C	neg or A to C
4 or 5	3	Low	Intermediate	Intermediate	0 or 1	neg or A
4 or 5	3	Low	Intermediate	High	2 or 3	B or C
		Braak 0-II	Braak III-IV	Braak V-VI		

The level of AD neuropathologic change is determined by assessing A, B and C scores. A scores are related to phases of Aβ deposition (first column), B scores to neurofibrillary Braak stages (bottom row) and C scores to CERAD stages (last column). Superimposed on the AD classification are criteria for "definite PART" (yellow) and "possible PART" (blue) based on the same information.

An evaluation of the NIA-RI criteria identified between 54 and 97% of AD cases with high Braak or CERAD stages, and eliminated between 60 and 100% of non-AD with low Braak or CERAD stages [232, 233]. Another autopsy study reported diagnostic sensitivity ranging from 70.9 to 87.3% and specificity from 44.3 to 70.8% [236].

The recent updated NIA/AA guidelines for the neuropathological assessment of AD consider ADNC levels regardless of the clinical history of a given individual [17]. They include (1) the recognition that ADNC may occur in the apparent absence of cognitive impairment; (2) the use of an "ABC" score for ADNC that incorporates histological assessment of Aβ plaques (A), based on its phase assessment [79], staging of NFTs, (B) based on the Braak staging system [231], and scoring of NPs, based on their semiquantitative assessment in at least three neocortical regions, and (C), based on CERAD criteria [230]. Table 2 shows how each of the three scores are transformed to state the level of ADNC on a four tiered scale (non, low, intermediate, and high). The entire process of the neuropathological diagnosis of AD can be followed along the pathways shown in Fig. 8. (3) More detailed approaches for assessing co-morbid conditions, such as Lewy pathology, vascular brain injury, TDP-43 immunoreactive lesions, argyrophilic grain dis-

ease, and others that can complicate the pathological diagnosis and can sometimes co-exist with AD, are also considered [17]. Testing of the revised NIA/AA guidelines in 390 autopsy cases distinguished pure AD and non-AD dementia from non-demented cases with a sensitivity of 91% and a specificity of 99%. The sensitivity increased after exclusion of non-AD dementia cases, indicating that the revised NIA/AA criteria appear practicable for distinguishing pure AD from non-AD dementia, preclinical AD, and controls [226]. The revised NIA/AA guidelines for the severity score for ADNC

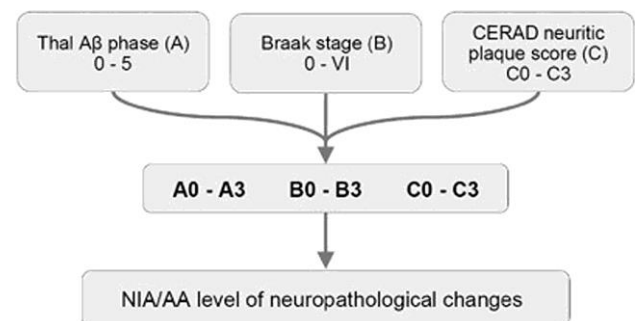


Figure 8. Pathway of the combination of different pathological features that allows a classification of ADNC according to the NIA-AA guidelines.

Table 3. Hypothetical correlation between PART and AD. From [253].

	No AD/no PART	Asymptomatic PART	p-preAD	NFT-predominant dementia (symptomatic PART)	Symptomatic AD
A β phase	0	0–2	1–5	0–2	3–5
Braak-NFT-stage	0	I–IV	0–VI	III, IV	III–VI
Degree of AD pathology	No AD	No or low AD	Low–high AD	No AD or low	Intermediate–high AD
Clinical signs of dementia or cognitive decline	No	No	No	Yes	Yes

PART vs. AD: symptomatic PART and symptomatic AD can be distinguished by A β pathology. Asymptomatic PART and p-pre-AD overlap in those cases with initial A β pathology (A β phases 1, 2)

used in the AD Centers Program achieved an excellent agreement ($\kappa=0.88$, 95% CI 0.77-0.95), and good-to-excellent agreement for the three supporting scores [237].

A comparative study of clinical and neuropathological diagnoses of AD in three epidemiological samples reported a sensitivity for probable AD of 93% [238]. Meta-analysis of 20 (out of 1,189) studies to distinguish autopsy-verified AD from other dementias or healthy controls showed a sensitivity of 85.4% (95% CI 80.8-90%) and a specificity of 77.7% (95% CI 70.2-85.1%). Values were higher for neuroimaging procedures and slightly lower for CSF biomarkers, while the combination of both resulted in better results [239].

3. Pathobiological subtypes of AD

Recent studies showed that the neuropathology of AD is heterogenous [240-242]. The current guidelines for the neuropathological diagnosis of AD only consider the classical “plaque and tangle” phenotype but not other subtypes such as the “plaque only but without tangle formation/predominant” type with abundant amyloid, or the “little or no tau pathology” type limited to the hippocampus and abnormal hp-tau in neocortical pyramidal cells. This type, observed in 3.4-8.0% of demented subjects over age 85 years [243], frequently represents a specific type of dementia with

Lewy bodies (DLB)/DLB-AD [244]. The recently described “primary age-related tauopathy” (PART) [245], previously referred to as “NFT-predominant dementia” [246], involves people over 85 years old and is associated with mild to moderate cognitive impairment [247, 248]. It reveals tau pathology restricted to the MTL (Braak stages 0-IV), relative absence of amyloid (Thal A β phases 0-2), total absence of NPs, and rare CAA [249]. The composition of NFTs in PART both for 3R and 4R tau isoforms is identical with those in classical AD [246], while pattern of hippocampal tau pathology differs significantly between PART and AD [250, 251]. Tau aggregates influence cognition and hippocampal atrophy in the absence of A β [249]. Positive correlations were reported in PART between the Braak NFT stage and phosphorylated 43-kDa TAR DNA-binding protein (pTDP-43) stage and density [252]. PART is considered either a prodromal form or a subtype of AD [253, 254] (see Table 3). MAPT H1H1 genotype frequency is high in both PART and limbic-predominant AD (LP-AD), and similar to typical AD, while APOE ϵ 4 is rather rare in PART [255]. Other genetic differences between PART and AD have been described [256]. It seems that lower concentrations of A β Os cause less severe tau deposition due to the fact that they can potentiate tau aggregation by promoting tau seed uptake [170]. Cognitive decline in PART is usually milder than in AD and correlates with tau burden. Biomarkers and neuroimaging studies will be important to define PART

ante-mortem and to follow its natural history [257]. While the incidence of classical AD increases from the 7th to the 9th decade and later shows a mild decrease, the frequency of PART increases after the age of 85 years [3].

The limbic-predominant age-related TDP-43 encephalopathy (LATE), a recently described disease entity mainly involving elderly people (>75 years at death), is associated with an amnesic dementia syndrome that may mimic AD [258, 259]. It shows pathogenic mechanisms of both frontotemporal lobar degeneration with TDP-43 (FTLD-TDP) and AD, but there are different molecular patterns of TDP-43 pathology in various clinical phenotypes with a higher chance of FTD-like symptoms in AD + full-length TDP-43 cases [32]. Recent studies indicated that in most cases, limbic-predominant age-related TDP-43 encephalopathy (LATE-NC) and FTLD-TDP can be differentiated by applying single neuropathological criteria, e.g., the severity of cortical TDP-43 inclusions [260]. Biomarkers for *ante-mortem* diagnosis of this syndrome are currently not available [261].

Recent clinicopathological studies have enabled the identification of several pathophysiologically defined subtypes of AD. One distinguished three AD subtypes based on NFT density: typical AD with balanced NFT counts in the neocortex and hippocampus (75%), hippocampal sparing (HcSp), with NFT counts predominantly in association cortices (11%), and limbic-predominant (LP) AD mainly involving the hippocampus (14%) [262]. These subtypes had different clinical phenotypes, with different ages at onset and rates of progression (Fig. 9). Patients with hippocampal sparing AD (HcSp-AD) were youngest at onset, had a higher proportion of men, and progressed more quickly than typical AD. LP-AD patients were older, more often female, and showed slower progression. Age at death of the LP form was highest, while patients with HcSp-AD were youngest, indicating this type as the most aggressive. This could be related to the contribution of TDP-43 pathology, hippocampal sclerosis, and the microtubule-associated protein tau (MAPT) H1H1 genotype to LP-AD, factors related to temporal lobe atrophy, older age, and slower disease progression. APOE ϵ 4 carriers more frequently had LP-AD and typical AD, whereas non-carriers more

frequently presented as HcSp-AD. Vascular co-pathology (ranging from 16 to 36%) was highest in the LP and lowest in the HcSp cases. Typical AD had higher AP burden in occipital regions compared with LP-AD [262], while in contrast to specific tau accumulation and brain atrophy patterns among AD variants, A β accumulation appeared rather diffuse and similarly across groups, except the MA group [263, 264]. Tau pathology was closely associated with sites of neurodegeneration and brain atrophy corresponded well with NFT topography and neuronal loss. [265-267]. Clinical symptoms correlate with neuronal hypometabolism [262, 268, 269]. Similar results were reported in a study of 933 autopsy cases of AD, all with neuritic Braak stage > IV [270]. Typical AD was more frequent than in the Mayo series (82.5 vs 75%), while the other two subtypes were slightly less frequent. Minimal-atrophy AD (MA-AD) was not included in this study. The LP-AD cases shared some morphological features with PART [245], although later studies demonstrated significant pathological differences between PART and LP-AD [240].

Typical AD showed greater white matter hyperintensity (WMH) burden, which may be due to Wallerian degeneration induced by cortical tau pathology [271, 272], small vessel disease, or both [273-275]. Tau pathology and neurodegeneration can disrupt key brain networks, which may induce memory impairment comparable to LP-AD and typical AD in the absence of overt brain atrophy of the MTL in MA-AD that shows [276-278]. Distinct patterns of NFT deposition in young-onset versus older-onset AD give evidence for variability in regional deposition patterns and demonstrate that different disease phenotypes have different patterns of tau pathology [279].

Other atypical non-amnesic syndromes, referred to as focal AD [26, 280, 281], include logopenic primary progressive aphasia (LPPA), showing higher NFT density in superior temporal gyrus but Thal amyloid plaques similar to amnesic AD [282-284]. The proportion of APOE ϵ 4 carriers was elevated in amnesic but not in non-amnesic forms of AD, suggesting that APOE is a selective risk factor that increases the vulnerability of memory-related medial temporal areas rather than language-related neocortices [285]. Further atypical forms

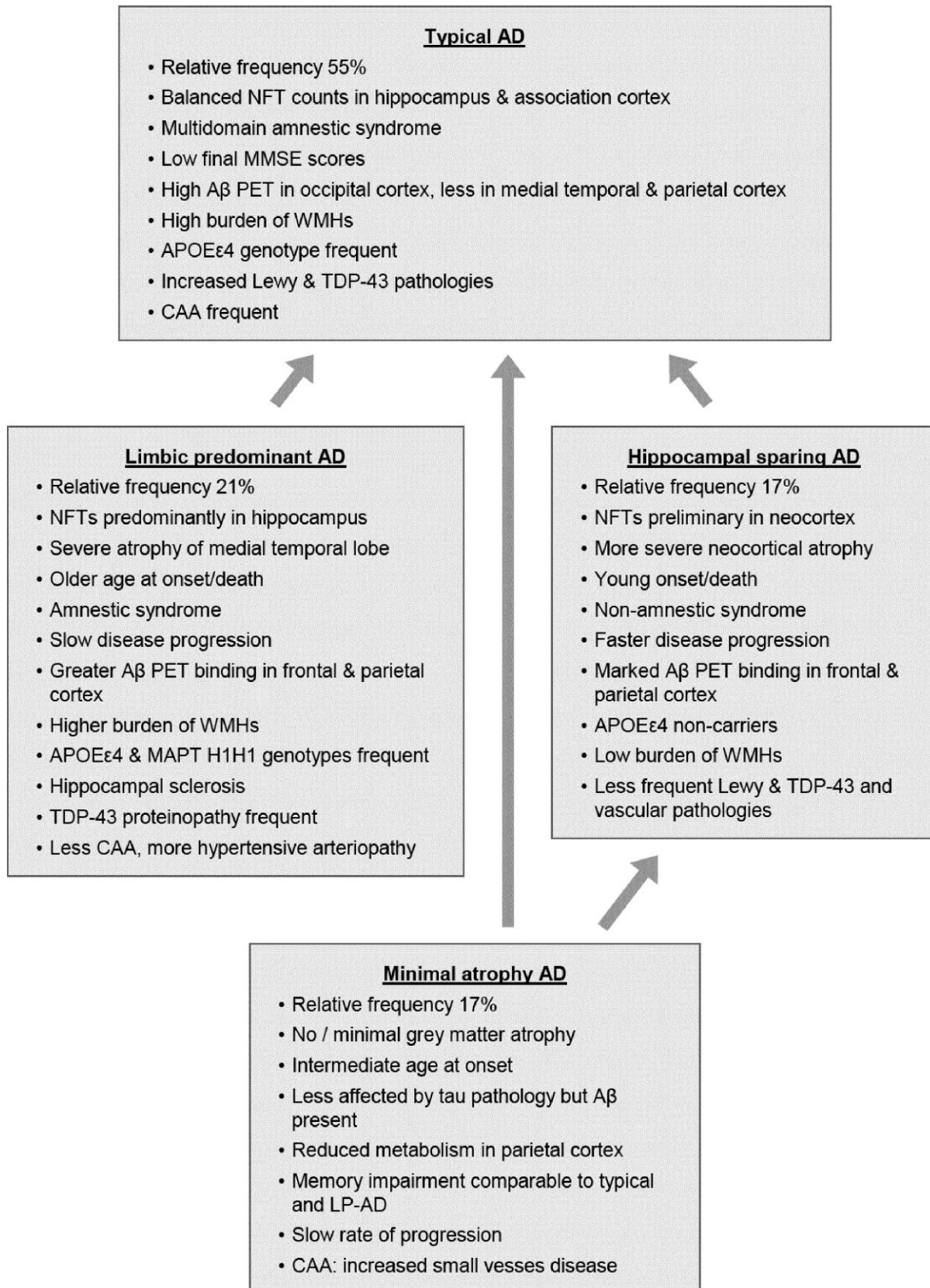


Figure 9. Main factors and characteristics of the four major subtypes of AD. AD: Alzheimer's disease; NFT: neurofibrillary tangle; WMH: white matter hyperintensity; CAA: cerebral amyloid angiopathy; EOAD: early-onset Alzheimer's disease; LOAD: late-onset Alzheimer's disease; LP-AD: limbic-predominant AD.

are posterior cortical atrophy (PCA) [286], non-amnesic AD with TDP-43 pathology [287], syndromes resembling behavioral variant frontotemporal lobe degeneration with tau pathology (bvFTD-tau) [266, 288], and the corticobasal syndrome (CBS) subtype of AD that shows a higher NFT density in the perirolandic cortices and greater neuronal loss in substantia nigra which may contribute to parkinsonism that uncommon in classic AD [289]. Behavioral/dysexecutive AD revealed temporo-parietal-predominant atrophy. In the Mayo series, PCA, LPPA and bvFTD variants were more common in HcSp-AD than in LP and typical AD [262, 290]. Accumulation of NFTs and activated hypertrophic microglia associated with low neuron densities suggests that they may collectively contribute to focal neurodegeneration characteristic of primary progressive aphasia AD [291].

The pathogenic factors underlying AD subtypes are unclear and cannot be explained by A β pathology alone, because the distribution of A β PET retention is quite similar in all subtypes [263]. However, solid-state nuclear magnetic resonance measurements showed qualitative differences between A β -40 and A β -42 aggregates in the brain tissue of patients with two atypical AD clinical subtypes - posterior cortical atrophy variant and a typical prolonged-duration form - indicating that there are structural variations in A β fibrils from AD clinical subtypes [60]. MA-AD, although A β -positive, shows less tau pathology. According to recent studies, AD "subtypes" may be linked to different tau protein modifications, suggesting that AD patients may have multiple molecular drivers of an otherwise common phenotype [192]. This suggests that multiple subtypes are parts of the same AD continuum [266], which may have consequences for personalized therapeutic approaches.

4. The impact of co-pathologies

AD pathology rarely occurs in isolation, while complex pathologies frequently lead to cognitive decline. The number of co-morbidities increases in the aging brain, causing mixed pathologies [3, 248, 274, 292-298]. The challenges of pathological mimics and concomitant pathologies in the neuropathologic diagnosis of AD have been critically reviewed recently [174]. The most frequent co-pathologies

are cerebrovascular disease (CVD) and Lewy and TDP-43 proteinopathies [31, 258, 299, 300]. In a consecutive autopsy series of 2,060 elderly demented patients and those with the clinical diagnosis of AD, ADNC were present in 82.9% of all demented and in 92.8% of clinically diagnosed AD cases, but only 33.6% and 47.6%, respectively, showed pure ADNC (ABC 3/3/3). The others were either atypical AD forms or subtypes (including PART) (7 and 6%, respectively) or exhibited additional CVD (24.3%), Lewy (12.5%) or other mixed pathologies. Vascular dementia in this cohort accounted for only 12.2% and 3.3%, respectively; other non-AD pathologies were present in 7.2% and 3.7% [301]. Another study of demented elderly persons reported pure ADNC in only 31% and multiple pathologies in 63% [302]. A review of 12 studies with 3,574 patients, irrespective of the clinical symptoms, reported ADNC between 19% and 67%, Lewy pathologies in 6% to 39%, vascular pathologies in 28% and 70%, TDP-43 proteinopathy in 19% to 78% [290], hippocampal sclerosis between 3% and 13%, and mixed pathologies between 8% and 70% [295]. Among 447 patients with probable AD, only 3.13% showed pure ADNC, 27.3% AD+CVD + other, 3% AD + CVD, 7.6% AD + other degenerative lesions, and 47% AD+CVD + other neurodegenerative lesions [293]. This list of combinations is not complete and there are other combinations with rare entities that need specific attention [174]. Among 673 autopsy cases, including 320 demented, the majority showed mixed pathologies [274]. LATE-NC was present in 57% of AD cases and was associated with more rapid disease progression [259]. Increased TDP-43 pathology in typical AD and LP-AD compared to HcSp-AD [262] was due to a strong association between hippocampal sclerosis and TDP-43, but clinical presentation seemed to be driven by morphological subtypes and not by TDP-43 pathology [290]. Among 61 autopsy-proven AD cases, LATE-NC was present in 67.2% (AD, LATE-NC), however, it was not associated with an increase of the burden of early or late tau nor A β pathology. LATE-NC showed a lower final mini mental state examination (MMSE) score independent of tau pathology [303]. Among 172 autopsy-confirmed AD cases, 19% were classified as non-amnesic, 69% of which had typical ADNC, 31% were HcSp-AD, 36% TDP-43-positive, while there were no LP-AD cases [287]. In a recent study of 46

autopsy-confirmed AD cases, 63% exhibited LATE-NC (AD+) and a higher burden of hp-tau. This indicates a possible progression of the disease, whereas AD plus LATE-NC was not associated with differences in cognitive scores [304]. LATE-NC may also occur in isolation and has been viewed as a common brain disease in aging [258]. Among 574 individuals with complete measurements of MMSE and the Clinical Dementia Rating scale sum of boxes (CDR-SB) from 39 AD centers across the USA, 63% of those given the 'gold standard' diagnosis of AD, possessed either TDP-43 proteinopathy or CAA of sufficient severity to independently explain the majority of their cognitive impairment. A β and/or tau burden, particularly in Braak stages IV to VI, and small cerebral vessel disease may synergistically affect cognitive decline [305], and a significant interaction was found between Braak NFT stages, CAA status and cognitive decline, suggesting that there is a significant interaction between tau pathology and CAA on cognition within the AD clinical spectrum [306]. Hence, interventions targeting CAA may contribute to delay the onset of cognitive impairment, particularly in individuals with intermediate ADNC [307]. This suggests that many individuals diagnosed with AD may actually suffer from a mixed dementia, and therapeutic targeting AD-related processes only may have limited efficiency in these co-morbid populations [298].

Based on data from the NACC, 1,854 participants with a clinical diagnosis of AD and ADNC at autopsy (confirmed AD) were studied; 204 with the clinical AD diagnosis had no ADNC (AD-mimics), while 253 participants with negative clinical AD diagnosis had ADNC (unidentified AD). Compared to confirmed AD cases, AD-mimics (FTLD-tau, hippocampal sclerosis, cerebrovascular pathology, etc.) had less severe cognitive impairment [308]. Special practical considerations for the diagnosis of essential co-pathologies and their relations with AD were given recently [174].

Argyrophilic grain disease (AGD), a limbic-predominant 4R-tauopathy, with grain-like deposits in neuritic dendrites, oligodendroglial inclusions ("coiled bodies"), ramified astrocytes, and ballooned neurons in the amygdala, hippocampus and MTLs [309], represents an age-related disorder and has been reported in up to 25% AD cases [310], and

rarely occurs before the age of 75 [311]. Aging-related tau astroglialopathy (ARTAG) is defined by the presence of two types of tau-bearing astrocytes: thorn-shaped and granular/fuzzy astrocytes in the brains of old-aged individuals in different locations and anatomical regions (subependymal, subpial, perivascular, white and gray matter [312, 313].

Among additional pathological changes in AD is granulovacuolar degeneration (GVD), characterized as 3-5 μ m vesicles bound by a unit membrane, most frequently occurring in the pyramidal neurons of the hippocampus, usually in association with NFTs. Their origin and significance are unclear. Despite the strong association between tau aggregation and granulovacuolar degeneration body (GVB) formation [314], intracellular aggregates of proteins other than tau can also induce GVB formation, which needs further elucidation [315]. The granule of the GVD is immunolabeled by antibodies against tubulin, ubiquitin, neurofilament, and tau [31]. They correlate with NFT density, suggesting that they may be a cellular response to neuronal damage or late-stage autophagic vacuoles [316]. Necrosome complex detected in GVD is associated with neuron loss in AD [317].

Recent clinicopathological studies have shown that the complex cascades of the underlying pathologies in most elderly patients may lead to cognitive decline, and that the number of possible combinations due to co-morbidities increases with aging [248]. These concomitant pathologies may be harmful to individuals with low cognitive reserve such as patients with MA-AD. They can cause a number of challenges including the evaluation of the significance of each pathological entity in the manifestation of the clinical symptoms, and the threshold of each individual pathology to cause dementia [174]. Total burden of comorbid pathological abnormalities, rather than any single lesion, is the most important cause of cognitive impairment, often despite clinical diagnosis of "only" AD [318].

5. Conclusions

AD is a heterogeneous, multifactorial disorder, manifesting clinically and morphologically as several subtypes that have a distinct signature of network disruptions associated with their atrophy pattern and reflecting the differential spread of NFT pathology and neuronal loss due to different vulnerability patterns of affected brain regions, which relates to specific molecular-functional properties of the affected neuronal systems [22, 23]. The severity of lesions corresponds to the “N” category in the new A/T/N classification for biomarkers [319]. The heterogeneity of the Alzheimer’s syndrome is related to multiple pathogenic factors which induce misfolding tau, A β , TDP-43, and other proteins, the synergetic or additive action of which results in various disease phenotypes [320]. Several factors such as brain resilience may help compensate for these pathologies up to a certain level, although their relevance is still poorly understood. These problems and the increasing incidence of AD illustrate its consequences on public health and the resulting challenges for future medicine. Increased sensitivity and specificity of new ATN biomarker systems and more extensive clinicopathological studies in well-defined populations are needed, with post-mortem studies using the updated NIA/AA criteria. The recent advent of tau PET and novel imaging and fluid-based (CSF) biomarkers allows us to study the temporal progression of tau pathology *in vivo* [321, 322]. Improving methods for disease detection and monitoring its progression may hopefully lead to the

development and refinement of tau-based therapeutics. In the interest of optimizing the clinical diagnosis of AD and related disorders, neuropathological studies should use a wide range of molecular pathological methods and should evaluate multiple CNS regions. An optimal and less cost-intensive strategy would be to screen specifically neurodegeneration-related proteins and to examine their cross reactions. The recent correlative work on concomitant pathologies has provide insight into the interactions of the various pathologies and their roles in causing dementing symptoms. Interdisciplinary studies may improve our knowledge about the pathogenesis of the heterogeneous manifestation of AD and promote methods for its early diagnosis as the basis for further preventive and successful disease-modifying therapeutic measures.

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Conflicts of Interest

The author declares no conflict of interest.

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