

## REVIEW

# Hypothesis review: Alzheimer's overture guidelines

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## Abstract

National Institute on Aging–Alzheimer's Association definition and classification of sporadic Alzheimer's disease (sAD) is based on the assumption that  $\beta$ -amyloid drives the pathogenesis of sAD, and therefore,  $\beta$ -amyloid pathology is the *sine-qua-non* condition for the diagnosis of sAD. The neuropathological diagnosis is based on the concurrence of senile plaques (SPs) and neurofibrillary tangles (NFTs) designated as Alzheimer's disease neuropathological changes. However, NFTs develop in the brain decades before the appearance of SPs, and their distribution does not parallel the distribution of SPs. Moreover, NFTs are found in about 85% of individuals at age 65 and around 97% at age 80. SPs occur in 30% at age 65 and 50%–60% at age 80. More than 70 genetic risk factors have been identified in sAD; the encoded proteins modulate cell membranes, synapses, lipid metabolism, and neuroinflammation. Alzheimer's disease (AD) overture provides a new concept and definition of brain aging and sAD for further discussion. AD overture proposes that sAD is: (i) a multifactorial and progressive neurodegenerative biological process, (ii) characterized by the early appearance of 3R + 4Rtau NFTs, (iii) later deposition of  $\beta$ -amyloid and SPs, (iv) with particular non-overlapped regional distribution of NFTs and SPs, (v) preceded by or occurring in parallel with molecular changes affecting cell membranes, cytoskeleton, synapses, lipid and protein metabolism, energy metabolism, neuroinflammation, cell cycle, astrocytes, microglia, and blood vessels; (vi) accompanied by progressive neuron loss and brain atrophy, (vii) prevalent in human brain aging, and (viii) manifested as pre-clinical AD, and progressing not universally to mild cognitive impairment due to AD, and mild, moderate, and severe AD dementia.

## KEYWORDS

Alzheimer's disease, genetics, human brain aging, membranes, neurofibrillary tangles, risk factors, senile plaques, tau,  $\beta$ -Amyloid

## 1 | THE BEGINNING: PRE-SENILE DEMENTIA, SENILE DEMENTIA, AND NORMAL BRAIN AGING WITH ALZHEIMER-LIKE CHANGES

In the first decade of the 20th century, the use of the Bielschowsky silver staining permitted the discovery of neurofibrillary tangles (NFTs) and senile plaques (SPs) by

Alois Alzheimer in a woman with pre-senile dementia [1], and by Oskar Fischer in cases with senile dementia [2, 3].

Alzheimer's disease (AD), including pre-senile and senile cases, was defined in 1984 as a neurodegenerative disease manifested by progressive dementia and characterized by brain atrophy, neuronal death, and a particular distribution of abundant SPs and NFTs in the brain [4].

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NFTs in the hippocampus, entorhinal cortex, inferior temporal cortex, and, very rarely, the frontal neocortex, together with more variable presence and distribution of SPs, in old-aged non-demented individuals, were considered normal brain aging [5–8].

In the early 90s, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) proposed a neuritic plaque score based on the number of SPs per mm<sup>2</sup> and the individual's age as a predictor of dementia to distinguish normal brain aging from AD [9, 10]. NFTs were not considered in this score.

## 2 | $\beta$ -AMYLOID AND TAU PATHOLOGY; FAMILIAL AND SPORADIC AD

In the middle 80s and early 90s,  $\beta$ -amyloid was identified as the primary component of SPs and  $\beta$ -amyloid cerebral angiopathy (A $\beta$ -CAA) [11–14].

At the same time, abnormal tau protein was identified as the main component of NFTs [15–19]. Abnormal tau in AD comprises the six 3Rtau and 4Rtau isoforms resulting from *MAPT* (microtubule-associated protein tau) splicing [20]. Abnormal tau also shows post-translational modifications such as hyper-phosphorylation, acetylation, glycosylation, and nitration. Reshaped tau conformation, truncation, oligomerization, and aggregation are added through the generation of NFTs [21–26].

Mutations in *APP* ( $\beta$ -amyloid precursor protein), *PSEN1* (presenilin1), and *PSEN2* (presenilin2) were causative of early-onset familial Alzheimer's disease (EOFAD, or fAD) in about 10%–15% of early-onset AD (EOAD) cases. *APP*, *PSEN1*, and *PSEN2* encode membrane proteins, and all are involved in producing  $\beta$ -amyloid through the cleavage of APP by the combined action of  $\beta$ - and  $\gamma$ -secretases. Increased APP dosage was also causative of fAD and  $\beta$ -amyloid angiopathy [27–32]. However, mutations in *MAPT* do not give rise to AD.

These discoveries led to the  $\beta$ -amyloid cascade hypothesis, which supports the concept that the production of  $\beta$ -amyloid fibrils is the primary factor triggering NFT formation and AD progression [33]. Later, the harmful effect of  $\beta$ -amyloid was extended to  $\beta$ -amyloid oligomers in addition to fibrils [34, 35].

Transgenic mice bearing only pathogenic *APP*, *PSEN1*, and *PSEN2* mutations develop cerebral and vascular  $\beta$ -amyloidosis. Among these are APP/PS1 double Tg mice expressing a chimeric mouse/human amyloid precursor protein (Mo/HuAPP695swe) and a mutant human presenilin 1 (PS1-dE9); and 5XFAD Tg mice over-expressing mutant human amyloid beta (A4) precursor protein 695 (APP) with the Swedish (K670N, M671L), Florida (I716V), and London (V717I) fAD mutations along with human presenilin 1 (PS1) harboring two fAD mutations, M146L and L286V, but not NFTs; tau pathology is restricted to

dystrophic neurites of SPs in transgenic mice. However, Tg mice bearing  $\beta$ -amyloid-related mutations and tau gene mutations develop SPs and NFTs, as in 3xTg-AD (APP<sup>Swe</sup>,tauP301L) and (APP<sup>Swe</sup>,tauP301L/Lfa *Psen1*<sup>tm1Mpm</sup>). Therefore, transgenic mouse-bearing mutations linked to fAD are models of  $\beta$ -amyloidopathy but not AD. Adding *mapt* mutations in the  $\beta$ -amyloidopathy transgenic murine models is necessary to produce neuropathology similar to that seen in fAD.

Moreover, not all *APP* mutations causative of (A $\beta$ -CAA) and cerebral amyloidosis are accompanied by tau pathology as in the Dutch and Flemish inherited A $\beta$ -CAA. *APP* mutations causing primary cerebral hemorrhages are principally located within the A $\beta$  domain [36].

Furthermore, the  $\gamma$ -secretase complex may act on more than 90 substrates [37, 38]. The diversity of substrates at the cell membrane suggests that mutations in presenilin genes trigger  $\beta$ -amyloid processing and may affect other membrane-associated proteins. In this line, the *PSEN-1* M146L mutation is causative of fAD with Pick bodies [39]. A patient with a familial history of early-onset frontotemporal lobar degeneration carried the *PSEN-1* M146V mutation; the post-mortem neuropathological study disclosed  $\beta$ -amyloid plaques, NFTs, Pick bodies in the hippocampus and cortex, cortical gliose tangles, and ubiquitin-positive nuclear inclusions in white matter oligodendrocytes [40]. The Gly183Val mutation in *PSEN1* is associated with Pick's disease but not  $\beta$ -amyloid plaques [41].

In summary, APP, presenilin1, and presenilin 2 are involved in various cellular functions linked to cell membranes. It can be suggested that mutations in fAD genes may lead to complex membrane dysfunction beyond  $\beta$ -amyloidogenesis. Altered membrane structure and function may facilitate tau phosphorylation and disrupt many metabolic signals. Cellular models learn about alternative or complementary dysfunctional consequences of AD-linked mutated proteins and variants [42–45].

However, about 95% of patients with dementia due to AD are sporadic (sAD), and mostly they are older than those suffering from EOAD (late-onset Alzheimer's disease: LOAD). Genetic factors play variable roles in the genesis of sAD. Individuals with Down syndrome, caused by the presence of all or part of the third copy of chromosome 21, have large numbers of SPs and NFTs at the age of 40. Allele  $\epsilon$ 4 of apolipoprotein E (APOE) was the first identified low-penetrating genetic risk factor of sAD [46–48]. Currently, more than 70 genetic risk factors have been identified using genome-wide association studies in patients with clinical manifestations of sAD [49–55]. The products of these genes modulate lipid metabolism and cell membranes, cytoskeleton, and neuroinflammation [56]. A few gene variants appear to be involved in APP metabolism, mainly through their putative impact on membrane structure and protein cleavage.

Shockingly, tau pathology in sAD has also been considered a secondary tauopathy subjected to the driving forces of  $\beta$ -amyloid pathology following the amyloid cascade hypothesis.

### 3 | TAU AND $\beta$ -AMYLOID PATHOLOGY IN BRAIN AGING AND SAD

In the 90s, the systematic analysis of NFTs and SPs in post-mortem brains of non-demented and demented individuals revealed the natural distribution and progression of NFTs and SPs with age [57–61].

At cortical Braak and Braak stages I and II, NFTs appear in the entorhinal and transentorhinal cortex. At stages III and IV, NFTs progress to the hippocampus, temporal cortex, and limbic system nuclei. At stages V and VI, NFTs spread to most areas of the neocortex. The spreading of NFTs is accompanied by a dramatic increase in neurons with NFTs across stage progression [57–61]. The olfactory bulb and tract, and several nuclei of the brain stem, including the raphe nuclei and the locus coeruleus, are also affected by tau pathology at the first NFT cortical stages; the number of NFTs increases in these regions with the progression of the neurodegenerative process [62–66]. The occurrence of NFTs in selected brain stem nuclei is categorized as subcortical stages a-c [61].

The distribution of SPs differs from NFTs in brain aging and sAD [67]. Stages 0, A, B, and C of Braak define the progression of SPs in the neocortex. Stage A: low density of SPs, especially in the frontal, temporal and occipital cortex; stage B: SPs in the neocortical association areas and hippocampus; stage C: in primary sensory and motor areas [57, 59, 61]. Thal's proposal categorizes phase 1: exclusively neocortex; phase 2: also allocortex; phase 3: diencephalic nuclei, striatum, and cholinergic nuclei of the basal forebrain; phase 4: brain stem; and phase 5: also the cerebellum [67].

The time of appearance of NFTs also differs from that of SPs. NFTs are identified in specific brain regions in young people in their twenties. The number of NFTs increases with age and affects about 85% of human beings at the age of 65, at least restricted to NFT stages I–III. About 98% of individuals have NFTs in the telenchalon at 80 [60, 61, 63, 68, 69]. In contrast, only about 30% have SPs at age 65 [57, 59, 61, 68, 69], and in around 60% over 80 [61]. NFTs without SPs are detected in about 35% of individuals older than 90 [61, personal observation].

The lack of temporal and regional concordance between NFTs and SPs is intuitively hardly consistent with the  $\beta$ -amyloid cascade hypothesis in brain aging and sAD [70, 71]. However, this scenario does not contradict the evidence that tauopathy is fueled by amyloid precursor protein dysfunction [72, 73].

AD is unique to humans. Other species may have scattered  $\beta$ -amyloid deposits and tau pathology, but in

none of these do SPs and NFTs show the prevalence, localization, and widespread distribution they manifest in human beings. Even so, the presence of tau pathology and  $\beta$ -amyloid deposits in certain old-aged animals points to a link between brain aging and abnormal tau and APP metabolism in many species, including dogs, bears, pinnipeds, primates, and cetaceans.

### 4 | REDEFINITION OF sAD IN THE SECOND DECADE OF THIS CENTURY: NATIONAL INSTITUTE ON AGING–ALZHEIMER'S ASSOCIATION GUIDELINES

Clinical and post-mortem neuropathological sAD progression suggests a concatenation of Alzheimer's disease neuropathological changes (ADNC, covering SPs and NFTs) in sAD [57–61, 69, 74–80]. This situation prompted a clinical redefinition of AD at the beginning of the second decade of this century by the National Institute on Aging–Alzheimer's Association (NIA-AA).

Three pillars underlay this new approach: (a) the neuropathological evidence of ADNC; (b) biochemical and neuroimaging biomarkers; and (c) clinical symptoms.

#### 4.1 | Neuropathology

NIA-AA guidelines considered SPs and NFTs essential neuropathologic features of AD [81–82]. The main points were (1) the recognition that ADNC may occur in the apparent absence of cognitive impairment; (2) the consideration of an “ABC” score for ADNC, incorporating histopathologic assessment of  $\beta$ -amyloid deposits (called A, based on Thal phases), staging of NFTs (called B, based on Braak stages), and scoring of neuritic plaques (called C, based on CERAD); and (3) the assessment of co-morbid conditions such as Lewy body disease, vascular brain injury, hippocampal sclerosis, and TDP-43 proteinopathy that may modify the clinical presentation in every particular individual.

NIA-AA guidelines assume that the appearance of SPs is the *sine-qua-non* condition for the neuropathological diagnosis of sAD. The presence solely of NFTs is not considered a prime manifestation of sAD [81, 82]. This way of thinking is based on the  $\beta$ -amyloid cascade hypothesis as the origin and trigger component of AD.

#### 4.2 | Biomarkers

Current cerebrospinal fluid (CSF), plasma, and blood biomarkers used in AD diagnosis are  $\beta$ -amyloid species, phospho-tau and tau, phospho-tau ratio, neurofilaments, synaptic proteins, activated astrocytes, and inflammatory markers [83–90]. The available methods cannot detect

differential levels of tau, phospho-tau,  $\beta$ -amyloid, and structural or synaptic proteins unless the degenerative process is at least at the middle stages of ADNC (A2, B2, C2, following the ABC score).

CT and MRI reveal that hippocampal atrophy is a late marker of AD that is only positive when there is advanced NFT pathology and neuron loss in the hippocampus.  $^{18}\text{F}$ -Fluorodeoxyglucose *positron emission tomography* ( $^{18}\text{F}$ -FDG *PET*) and fMRI may detect hypo-perfusion and hypo-metabolism linked to neuronal function.

PET using specific radiotracers permits the visualization of abnormal protein deposits, particularly  $\beta$ -amyloid and P-tau species. A recent meta-analysis revealed that ~25%–35% of cognitively normal older adults harbored a significant amount of  $\beta$ -amyloid [91].

Tau-PET shows early tau deposition in the entorhinal and temporal cortices in  $\beta$ -amyloid-negative non-demented individuals and its progression to other brain regions following more advanced NFT Braak stages in individuals with added  $\beta$ -amyloid pathology [92–99]. Tau-PET is considered a promising tool for better prediction of cognitive change than amyloid-PET and MRI, and it may support the prognostic process in the pre-clinical stages of AD [100].

PET studies, and particularly tau-PET observations, confirm that: (i) tau pathology precedes by several decades the appearance of  $\beta$ -amyloid in brain aging without cognitive impairment; (ii) tau pathology may be found in some individuals suffering from cognitive impairment without concomitant  $\beta$ -amyloid deposition, and; (iii) tau pathology, rather than  $\beta$ -amyloid pathology, correlates with progressive cognitive decline in sAD.

#### 4.3 | Clinical classification of Alzheimer's disease

A critical historical misunderstanding regards the term Alzheimer's disease (AD) as synonymous with Alzheimer's dementia. However, a significant achievement in understanding AD as a clinically progressive neurodegenerative process was formalized at the beginning of the second decade of this century by the NIA-AA. Clinically AD was categorized as pre-clinical AD, MCI due to AD, and mild, moderate, and severe Alzheimer's dementia [83, 101–116, and <https://www.alz.org/media/Documents/Alzheimer's-facts-and-figures>].

Pre-clinical AD is considered in individuals with measurable brain changes revealed by biomarkers that indicate the earliest signs of AD but have not yet developed symptoms such as memory loss. MCI due to AD is considered in people with biomarker evidence of ADNC plus new but subtle signs such as memory, language, and thinking problems. Pre-clinical AD is contemplated as a biological situation that makes possible, but not obligatory, the appearance of dementia later in life in the context of ADNC.

The selection of biomarkers by the NIA-AA is in line with the creed of the  $\beta$ -amyloid cascade hypothesis. Pre-clinical stage 1 is characterized by primary amyloidosis and assessed by the positivity of  $\beta$ -amyloid biomarkers and negativity of tau biomarkers. Stage 2 is asymptomatic cerebral amyloidosis plus “downstream” neurodegeneration based on high CSF tau/P-tau ratio, neuronal dysfunction, cortical thinning, and hippocampal atrophy. Pre-clinical stage 3 is distinguished by cerebral amyloidosis, neurodegeneration, and subtle cognitive decline.

The early presence of positive tau-PET in the inner regions of the temporal cortex in the absence of positive  $\beta$ -amyloid markers does not merit the categorization of pre-clinical AD according to the current definition of the NIA-AA.

However, cognitive status correlates with NFT burden rather than  $\beta$ -amyloid plaques [107].

## 5 | PRIMARY AGE-RELATED TAUOPATHY

The term “primary age-related tauopathy” (PART) was coined to include cases with NFT pathology at stages I–IV of Braak in the absence of  $\beta$ -amyloid plaques [108]. Patients are cognitively “normal for age” or maybe suffer from MCI; dementia is rare [108–111]. Early tau pathology without  $\beta$ -amyloid deposits can be detected by tau-PET, thus allowing a clinical identification of the pathology during life [96, 99, 100]. PART is predominant until the age of 60–70, prior to the progressive appearance of SPs in the brain. At this point, the incidence of AD increases at the expense of reduced incidence of PART. Thus, AD prevails in individuals aged 80–90, whereas NFT-only pathology accounts for about 20% of the population. Dementia only with tangles (or tangle-predominant dementia), which would be the logical progression of PART, is very uncommon [112].

Genetic studies carried out in neuropathologically-verified PART cases have shown a lower prevalence of *APOE $\epsilon$ 4*, rs28834970 *PTK2B*, rs6733839 in the *BINI*, and *CRI* genes, and a higher prevalence of *APOE $\epsilon$ 2* [110, 113, 114]. In contrast, tangle-predominant dementia has been associated with the *MAPT H1* haplotype [115]. The proposal of PART as a new tauopathy is not widely accepted; PART is also interpreted as part of AD [61, 116, 117].

## 6 | BRAIN ALTERATIONS IN THE AGING FRONTAL CORTEX AND SAD ARE NOT RESTRICTED TO NFTs AND SPs, AND THEY MAY PRECEDE ADNC

Molecular changes in brain aging and sAD are not restricted to  $\beta$ -amyloid and abnormal tau accumulation. Multiple systems are primarily dysfunctional or

secondarily damaged by abnormal  $\beta$ -amyloid and tau species. Added molecular changes compromise: (i) synapses; neurotransmitters, neuromodulators, and related receptors, including acetylcholine and acetylcholine receptors, glutamate and glutamate receptors,  $\gamma$ -aminobutyric acid (GABA) and GABA receptors, serotonin and 5-hydroxytryptamine (5-HT) receptors, noradrenergic system, adenosine receptors, endocannabinoids, cannabinoid receptors, endorphins, and orexin; (ii) trophic factors and receptors; (iii) mitochondria and oxidative phosphorylation; (iv) oxidative and nitrosative stress damage to lipids, nucleic acids, and proteins; (v) mitochondria/endoplasmic reticulum interactions; (vi) endoplasmic reticulum stress; (vii) failure of the ubiquitin-proteasome system and autophagy to remove debris; (viii) granulovacuolar degeneration; (ix) purine metabolism; (x) histone modifications, DNA methylation, and hydroxymethylation; (xi) non-coding RNAs; (xii) protein synthesis; (xiii) altered cell cycle and re-entry; and (xiv) cell death. Other key elements in the pathogenesis of brain aging and sAD are early dysfunctional astrocytes and microglia, followed by altered oligodendrocytes; and alterations in the neurovascular system manifested as early reduction of the cerebral blood flow and abnormal blood barrier function. All these factors, together with  $\beta$ -amyloid and tau, contribute to neuronal cell death and reduced neuronal connectivity [69, 118–120].

Notably, several of those determining molecular changes linked to brain aging and sAD precede the appearance of NFTs and SPs, as demonstrated by their occurrence in brain regions not affected by SPs and NFTs at NFT stages I and II. Molecular changes progress with particular profile-, time-, and region-dependent patterns [120]. Molecular changes have deleterious effects on brain functions, involving various structures and pathways. Most of them may participate in the later development of tau pathology and  $\beta$ -amyloid production [120].

NFTs and  $\beta$ -amyloid, in turn, potentiate all the above-mentioned molecular alterations, thereby creating positive feedback for the degenerative process [120]. Other putative factors influencing brain aging and sAD, categorized as environmental factors, include oral cavity infections, intestinal microbiota, intellectual reserve, diet, and good health [120].

Table 1 summarizes molecular changes in the frontal cortex and hippocampus in sporadic cases at NFT stages I and II.

## 7 | TOWARDS AN ALTERNATIVE INTERPRETATION OF BRAIN AGING AND sAD: A NEW DEFINITION OF AD

The natural history of ADNC changes during the human lifespan shows the early formation of NFTs, followed by the appearance of  $\beta$ -amyloid deposits decades later [57–61, 69]. This fact has been interpreted in two ways.

Defenders of the  $\beta$ -amyloid cascade hypothesis, represented by the NIA-AA, split the process into two diseases: AD and PART. Other researchers postulate that tau pathology is an initiating factor in sAD [61]. However, there is no 3R tauopathy or 4R tauopathy and no other sporadic 3R + 4R tauopathy linked to the generation and deposition of  $\beta$ -amyloid. Therefore, it is speculative to posit that tau pathology sets off  $\beta$ -amyloid production in sAD, even though NFTs are the first ADNC in human brain aging [61].

Another proposal suggests the existence in the human brain of a PART to which  $\beta$ -amyloid deposition is added in a time-, rate- and region-dependent manner in the different AD categories, reliant on genetic factors involved in the production of  $\beta$ -amyloid [121].

Not surprisingly, the mutually exclusive hypotheses formulated to explain sAD are not satisfactory and have not produced significant beneficial results when applied in clinical trials. In short, anti- $\beta$ -amyloid therapies have been unsuccessful not because they cannot reduce  $\beta$ -amyloid deposits, as they indeed do, but rather because they do not stop the progression of the disease. In addition, therapies geared to reducing abnormal tau deposits face difficulty picking up the critical tau species, which may block NFT formation. Moreover, current therapies do not contemplate actions directed to the multiple genetic and molecular factors, which are indeed the inducers of ADNC.

A new concept and definition of brain aging and sAD are brought forward for further discussion. AD overture guidelines advance that sAD is: (i) a multifactorial and progressive neurodegenerative biological process, (ii) characterized by the early appearance of 3R + 4Rtau NFTs, (iii) later deposition of  $\beta$ -amyloid and SPs, (iv) with particular non-overlapped regional distribution of NFTs and SPs, (v) which are preceded by, and occurring in parallel with, molecular changes involving determining sub-cellular structures and functions; (vi) accompanied by progressive neuron loss and brain atrophy, (vii) prevalent in human brain aging, and (viii) manifested as pre-clinical AD, and progressing not universally to mild cognitive impairment due to AD (MCI-AD), and mild, moderate, and severe AD dementia (ADD).

The neuropathological characteristics and clinical correlates of sAD overture compared with NIA-AA guidelines are summarized in Figure 1.

The “ABC” score for ADNC proposed by the NIA-AA is helpful, but Braak  $\beta$ -amyloid scores are similar to CERAD neuritic plaque scores and might also be used to categorize the extension of plaques in the cerebral cortex. As a supplementary note, immunohistochemistry with validated antibodies against P-tau and  $\beta$ -amyloid is mandatory.

The critical point that distinguishes the AD overture definition from the NIA-AA proposal is the early appearance of tau pathology as the first neuropathological ADNC marker of sAD. The  $\beta$ -amyloid cascade hypothesis is no longer considered the cause of sAD. However,

**TABLE 1** Altered components, pathways, and functions in the frontal cortex and hippocampus at NFT stages I and II preceding the appearance of NFTs and SPs in these regions in cases with pre-clinical AD

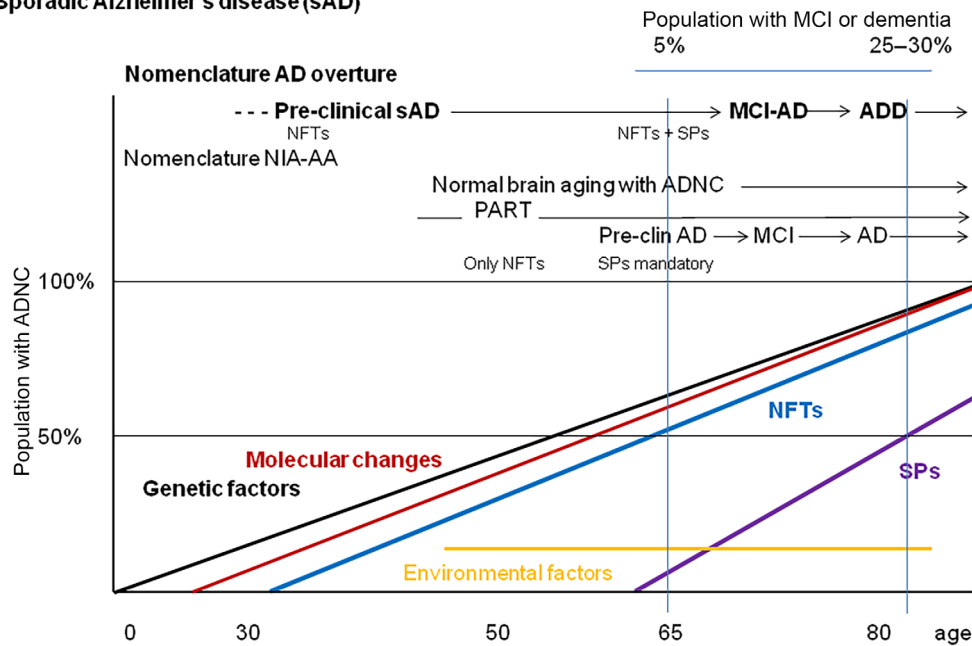
Main components	Main functional effects
Aberrant cell-cycle re-entry and altered adult neurogenesis	<ul style="list-style-type: none"> <li>Programmed cell death, activation of kinases, oxidative stress damage, tau hyperphosphorylation, activation of <math>\beta</math>-amyloid pathways, altered NGF/proNGF/p75 signaling</li> </ul>
Brain lipids	<ul style="list-style-type: none"> <li>Progressive decrease in the levels of cholesterol, phosphatidylethanolamine, phosphatidyl inositol, phospholipid, ethanolamine plasmalogen, and sphingomyelin; progressive modifications in the composition of PUFAs, and higher levels of MUFAs: altered brain composition, altered cell signaling, altered neuroinflammatory responses</li> <li>Modifications in DHA, AA, and PUFAs produce an imbalance between their protective role (the adaptive responses derived from their lipid mediators) and a deleterious role (derived from their susceptibility to oxidation)</li> <li>Cholesterol-derived lipid mediators, including 24- and 25-hydroxycholesterol, produce apoptosis</li> <li>Increased lipid peroxidation results in altered membrane function</li> <li>Increased lipofuscin</li> </ul>
Lipid rafts and cell membranes	<ul style="list-style-type: none"> <li>Altered lipid raft composition involving plasmalogens, PUFAs (especially DHA and AA), total polar lipids (mainly phosphatidylinositol, sphingomyelin, sulfatides, and cerebrosides), and total neutral lipids (particularly cholesterol and sterol esters) alter membrane composition and impair normal cell membrane signaling</li> <li>Altered cell membrane composition impacts cytoskeletal proteins through protein–protein interactions, electrostatic interactions with lipid membranes, and lipid tails</li> <li>Increment in local cholesterol increases BACE1/A<math>\beta</math>PP interaction and facilitates the production of <math>\beta</math>-amyloid</li> <li>Microglial pro-inflammatory mediators generate membrane damage</li> </ul>
Specialized membranes	<ul style="list-style-type: none"> <li>Altered synaptic membranes</li> <li>Altered expression of certain neurotransmitter receptors and modulators of neurotransmission</li> <li>Altered connectivity</li> </ul>
Mitochondria	<ul style="list-style-type: none"> <li>Altered mitochondrial membranes</li> <li>Altered OXPHOS</li> <li>Increased production of ROS</li> <li>Altered mitochondrial DNA methylation</li> <li>Impaired cross-talk between endoplasmic reticulum and mitochondria: altered MAM interaction</li> </ul>
Oxidative stress damage	<ul style="list-style-type: none"> <li>Mitochondria, peroxisomes, ER, microsomes, nucleus, and plasma membrane are potential sources of ROS</li> <li>Oxidative stress damage DNA, RNA, carbohydrates, lipids, and proteins</li> </ul>
Protein synthesis impairment	<ul style="list-style-type: none"> <li>Alterations of protein synthesis pathways at the level of the nucleolus, mRNAs, miRNAs, ribosomal proteins</li> </ul>
Dysregulated protein phosphorylation	<ul style="list-style-type: none"> <li>Dysregulated phosphoproteins at NFT stages I and II are membrane proteins; proteins of the cytoskeleton; proteins of the synapses and dense core vesicles; proteins linked to membrane transport and ion channels; kinases; proteins linked to DNA and protein deacetylation; proteins linked to gene transcription and protein synthesis, and proteins involved in energy metabolism</li> <li>Altered phosphorylation of selected proteins, accomplished by activation of several kinases, may alter membrane and cytoskeletal function, among these synaptic transmission and membrane/cytoskeleton signaling, in addition to energy metabolism, protein synthesis, and DNA homeostasis</li> </ul>
Inflammation	<ul style="list-style-type: none"> <li>Aging is accompanied by low levels of activated innate inflammatory responses</li> <li>Activated microglia showing increased expression of ApoE, triggering receptor expressed on myeloid cells 2 (TREM2), and lipoprotein lipase (LP2)</li> <li>Modified astrocytes: increased expression of glial fibrillary acidic protein (GFAP), S100<math>\beta</math>, and vimentin, and modifications in morphology and number</li> <li>Senescent astrocytes; senescence-associated secretory phenotype manifested by increased production of pro-inflammatory cytokines together with oxidative damage and increased superoxide production</li> <li>Early dysregulation of selected inflammatory mediators such as C3AR1, CSF1R, CSF3R, IL6, IL6ST, TGF<math>\beta</math>1, and IL10RA</li> <li>Different inflammatory responses occur simultaneously in different regions in the same individual</li> <li>Clinical evidence of the protective role of non-steroidal anti-inflammatory drugs at pre-clinical stages of AD</li> </ul>
Primary alteration of small cerebral blood vessels	<ul style="list-style-type: none"> <li>Altered endothelium, pericytes, composition of basal membranes, and altered function of podocytes</li> <li>Impaired CBF</li> <li>Impaired glucose uptake</li> <li>Impaired BBB</li> </ul>

Abbreviations: AA, arachidonic acid; BBB, blood–brain barrier; C3AR1, complement component 3a receptor 1; CBF, cerebral blood flow; CSF1R: colony-stimulating factor 1 receptor; CSF3R, colony-stimulating factor 3 receptor; DHA, docosahexanoic acid; IL10RA, interleukin-10 receptor; IL6, interleukin-6; IL6ST, interleukin-6 signal transducer; MAM, mitochondria-associated ER membranes; MUFAs, monounsaturated fatty acids; OXPHOS, mitochondrial oxidative phosphorylation system; PUFAs, polyunsaturated fatty acids; ROS, reactive oxygen species; TGF $\beta$ 1, transforming growth factor- $\beta$ 1.

the early appearance of tau pathology does not presuppose that tau pathology is the sAD's origin. As indicated in Figure 1, genetic factors and molecular changes

summarized in Table 1 are considered the earliest and complementary partners that induce tau and  $\beta$ -amyloid pathology at separate times of the lifespan.

## Sporadic Alzheimer's disease (sAD)



**FIGURE 1** Schematic representation of the natural history of ADNC and associated genetic factors, environmental factors, molecular changes listed in Table 1, NFTs, and SPs with age in years. The proposed AD overture diagnosis and staging are compared with NIA-AA guidelines. ADNC: Alzheimer's disease neuropathological changes; AD, Alzheimer's disease; ADD, AD dementia; MCI-AD, mild cognitive impairment due to AD; NFTs, neurofibrillary tangles; PART, primary age-related tauopathy; SPs, senile plaques. Major differences between NIA-AA guidelines and AD overture are the consideration of tau pathology as the first ADNC marker of AD; pre-clinical sAD is used instead of pre-clinical AD; the diagnosis of pre-clinical sAD is advanced by several decades based on the detection of tau pathology in the inner temporal cortex; normal brain aging with ADNC and PART are within the spectrum of sAD; molecular changes (most of them deserving in deep study) preceding, or occurring in parallel with, ADNC, converge at different times leading to neuronal and glial dysfunction, and act as inducers of ADNC; genetic factors have determining roles pointing to the relevance of lipid transport, membrane integrity, and neuroinflammation in the pathogenesis of sAD.

**TABLE 2** Comparison of staging categories for pre-clinical AD between the NIA-AA (A) and AD overture (B) guidelines

(A)					
Stage	Description	A $\beta$ -PET, low CSF A $\beta_{1-42}$	High CSF tau/P-tau, neuronal dysfunction (FDG-PET or fMRI), cortical thinning, hippocampal atrophy (sMRI)	Subtle cognitive decline	
1	Asymptomatic cerebral amyloidosis	Positive	Negative	Negative	
2	Asymptomatic cerebral amyloidosis + "downstream" neurodegeneration	Positive	Positive	Negative	
3	Cerebral amyloidosis + Neurodegeneration + Subtle cognitive decline	Positive	Positive	Positive	
(B)					
Stage	Description	Tau-PET	A $\beta$ -PET, low CSF A $\beta_{1-42}$	High CSF tau/P-tau, neuronal dysfunction (FDG-PET or fMRI), hippocampal atrophy (sMRI)	Subtle cognitive decline
1	Asymptomatic primary tauopathy	Positive	Negative	Negative	Negative
2	+Asymptomatic cerebral amyloidosis	Positive	Positive	Negative	Negative
3	+Positive CSF tau biomarkers, +cerebral dysfunction	Positive	Positive	Positive	Negative
4	+subtle cognitive decline	Positive	Positive	Positive	Positive

Abbreviations: A $\beta$ ,  $\beta$ -amyloid; FDG, fluorodeoxyglucose (18F); fMRI, functional magnetic resonance imaging; PET, positron emission tomography; sMRI, structural MRI.

Regarding the value of biomarkers suggested by the NIA-AA, AD overtone shifts to recognizing early tau pathology, mainly revealed by tau-PET, as the earliest marker of sAD. However, new indicators are needed to detect early molecular alterations preceding, or occurring in parallel with, tau and  $\beta$ -amyloid pathology. Among them, changes in protein and lipid composition of cell membranes, and altered membrane signaling with the cytoskeleton, mitochondria, and vesicles are significant targets for further research. Age-related astroglial and microglial alterations, modification of neuroinflammatory profiles, and cerebral blood vessel dysfunction with age are determining, as well.

Finally, the clinical classification of AD overtone also differs from the NIA-AA classification in categorizing pre-clinical sAD. Nevertheless, the terms MCI due to AD and mild, moderate, and severe Alzheimer's dementia are modified slightly in the new classification. MCI due to AD is named MCI-AD, and mild, moderate, and severe Alzheimer's dementia, are named mild, moderate, and severe ADD. ADD is introduced to avoid confusion between AD (Alzheimer's disease) and AD dementia (restricted to the most advanced AD phase).

Regarding pre-clinical sAD, AD overtone guidelines propose that stage 1 corresponds to asymptomatic primary tauopathy as revealed with high-resolution tau-PET. Stages 2–4 are similar to stages 1–3, respectively, proposed by the NIA-AA [83], but tau-PET is positive in every stage. The new staging and diagnostic criteria for pre-clinical sAD compared with the NIA-AA guidelines are summarized in Table 2A, B.

The concept of human brain aging and sAD proposed in AD overtone seems more closely adapted to the natural history of events during brain aging and sAD. AD overtone has additional clinical implications. The diagnosis of pre-clinical sAD has been advanced for several decades. Moreover, learning about molecular changes involving various structures and signaling pathways preceding or occurring in parallel with the appearance of tau pathology and  $\beta$ -amyloid deposition may be an opportunity to design new unconventional, breakthrough therapies.

AD overtone guidelines are centered on human brain aging and sAD. At present, we do not have enough information to apply the same parameters, particularly those linked to molecular brain changes at pre-clinical stages and pre-clinical biomarkers, to fAD caused by mutations in *APP*, *PSEN1*, and *PSEN2*.

## AUTHOR CONTRIBUTION

IF has written the paper.

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## CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

## DATA AVAILABILITY STATEMENT

No new data. All data are in the manuscript.

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