

Alzheimer's Disease: Recent Advances

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ABSTRACT

These days our society is combating against a neurodegenerative disease called Alzheimer's disease which is an age-related dementia. The concern has become graver as the disease may not be a necessary outcome in the oldest old and may even thrive in an age of thirties or forties. Alzheimer's impairs a person's cognitive ability and gradually leads to loss of bodily functions, making them dependent on others. Plaques and tangles are the two prime hallmarks in the disease progression. Their escalation in the cortex gradually causes shriveling up of the brain. Unfortunately, the neurodegenerative changes are irreversible and no treatment can retard the progression of the disease. New therapeutic interventions related to Alzheimer's disease are needed to be explored in order to apprehend the order of its occurrence and retard its progression.

Key words: Dementia; AD; Neurodegeneration; Progression; Clinical symptoms; Protein aggregation; Apoptosis; Amyloid plaques; Neuroinflammation; Preventions; Biomarkers

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INTRODUCTION

Alzheimer's disease (AD)^[1,2,3] is one of the most recurrent types of dementia which accounts for around 60-80 % of the cases of dementia^[4]. "Dementia" is a blanket term used to describe any brain disease that impairs a person's cognitive ability i.e. memory, behaviour and ability to think clearly^[5]. The other forms of dementia include Parkinson's disease^[6], Huntington's disease^[7], Lewy body dementia^[8], vascular dementia^[9], Creutzfeldt-Jakob disease^[10], frontotemporal dementia, progressive supranuclear palsy^[11,12] and normal pressure hydrocephalus^[13].

The different forms of dementia run counter in terms of the distinct pattern of symptoms and abnormalities in the brain. Alzheimer's Association published the definitions of the various forms of dementia, suggesting overlapping features in them^[14,15]. Dementia is neurodegenerative in nature and the associated conditions develop due to malfunctioning or death of nerve cells (called neurons) in the brain which may become more common with age. In AD, which is an age-related dementia, the neurodegenerative changes in brain gradually cause loss of basic bodily functions like speaking, walking and swallowing and, ultimately, prove to be fatal. It is a progressive ailment i.e. the degeneration in the structure and chemistry of the brain increases over time.

Cognitive aging and AD were explored in a review^[16]. It was suggested that the latter is critical to genetics and previous brain injuries and, although more prevalent in the aging population, it is not a necessary outcome only in the oldest old. Some believe environmental and intergenerative approaches can better incorporate "existent world" ecological and psychosocial models of health to recalibrate the study of the disease^[17]. Additionally, factors like education^[18], diet, exercise and cognitive stimulation all seem to make Alzheimer's more likely.

AD was first identified more than 100 years ago by a German psychiatrist and neuropathologist Alois Alzheimer and was named after him^[19,20,21]. Despite its long history, the research into its characteristics, pathophysiology, diagnosis, prevention, risk factors,

management and treatment has gained impetus only in the last few years. In spite of the wealth of research that has been reported during these years, the changes in the brain that stimulate the development of Alzheimer's and their order of occurrence largely remain a moot question. Therefore, this work is dedicated to review AD, the most common dementia in aging population, and to compile the recent advances in its ongoing research.

ONSET OF ALZHEIMER'S DISEASE

The categorization of AD is generally based on the differences in age of its onset and can be broadly classified as early-onset and late-onset AD. It can also be categorized as familial and sporadic AD on the basis of differences in the genetic cause^[22]. Neurologists generally have a belief that both have similar overall sequence of symptoms and increasing impairments.

Early-onset alzheimer's

Less than 10% of all AD subjects are pinpointed with the disease before age 65; this is referred to as early-onset *alzheimer's*. This is an uncommon form of AD, known to develop in a person's 30's, 40's, and 50's (and very scarcely in the late 20's). Ironically, early-onset AD patients are often not included in drug studies because of the young age. Approximately 13% of the cases of early-onset *alzheimer's* are *familial AD*^[23], that is, known to be entirely inherited. People with Down's syndrome^[24] or other autosomal-dominant inheritance are particularly at a risk for this form of AD. There are even the rarest of rare cases of non-familial early-onset AD that thrive in people of 30's or 40's.

Late-onset alzheimer's

Late-onset *alzheimer's* is the most prevalent type of AD which accounts for about the rest 90% of the cases, and usually occurs after age 65. Late-onset AD strikes almost half of all people over the age of 85 and may or may not be hereditary. Late-onset dementia is also called *sporadic AD*^[25], in which genetic and environmental differences may act as risk factors, exclusive of autosomal-dominant inheritance. The disease can also be associated with a genetically defected chromosome 14, to which late-onset AD is not related.

CLINICAL SYMPTOMS OF ALZHEIMER'S DISEASE

The 2011 proposed criteria and guidelines for diagnosis of AD^[26-29] suggest that AD begins 20 years or more before the occurrence of symptoms referred as the preclinical stage of AD or *asymptomatic stage* of AD. People seem to be free of any symptom but toxic changes start occurring in the brain by this time. Since there is no effective treatment to delay onset or prevent the disease, the focus has now shifted to identify and treat AD during the long preclinical stage. The destruction to nerve cells and tissues starts from the cerebral cortex. It is the region of the brain responsible for high-level brain functions such as consciousness, memory, language, reading and intelligence, which starts shriveling up. According to the results^[30], AD patients' oral reading is marked by reduction of speech and articulation rates, high number and proportion of pauses, and poor effectiveness of phonation time. All parts of the visual system may be affected, including the optic nerve and the retina^[31].

The area of the cortex, mainly hippocampus, which is responsible for the formation of the new memory, begins to shrink^[32], leading to short term memory loss, the first warning signs of cognitive loss,

demarcated as the early stage of AD. The condition is sometimes more pronounced with mild cognitive impairment (MCI). MCI, also called *prodromal stage* of AD, is the transition stage between preclinical stage and early AD. A trend of a slight increase of cerebral blood flow in both hippocampi and the posterior cingulate gyrus has been noticed in MCI patients with a decrease in AD patients^[33]. The MCI stage of the disease is detected through cognitive tasks like the mini-mental state examination and computerized screening instruments^[34]. At this stage of the disease, memory deficit becomes serious enough to be noticed by the subject or other people but at the same time does not hamper daily life or independent function.

Progression of Alzheimer's aggravates memory loss and evidently impairs other cognitive abilities, such as reasoning or judgment, vision, language and word-finding, leading to *dementia*. Memory loss and confusion grow worse, and people begin to have problems identifying family and friends. They may have difficulty to grasp new things, perform daily tasks or manage with new situations.

People are often diagnosed in the dementia stage^[26]. The incidence of dementia and AD is considered to be associated with neuropsychiatric symptoms^[35] and therapeutically targeting the latter might retard the conversion of MCI to dementia. Behavioral or non-pharmacologic treatment may represent another effort towards reduction of dementia risk in AD patients^[36,37]. A study revealed the existence of a poor perception of emotions in AD subjects^[38]. A distinct pattern was observed in visual and auditory-verbal perception, whereas only the verbal modality seems to be relatively preserved. Thus, strengthening of emotional prosody can be used as a communication support between the patient and care-givers.

Problem of apathy, hallucinations, paranoia and delusions^[39] make the patients more impulsive. These symptoms occur in approximately 50% of AD patients, indicative of a more severe phenotype. The risk for psychosis in AD is genetically mediated, as revealed by studies on familial aggregation of AD and psychosis^[40]. Baseline inferior temporal and supramarginal cortical thinning are predictive of worsening apathy and hallucination over time^[41]. Actigraphy can prove to be a fruitful complementary measurement in the clinical diagnosis of apathy related to AD^[42]. Delusions are clinically and neurobiologically related to memory deficits but partially. Likewise hallucination, delusion in AD, is linked with dysfunctioning of specific frontal and temporal cortex^[43].

Then, in the *early stages* of AD, the alterations in plaques and deposition of tau proteins start taking place. A dramatically high loss of nerve cell and synapse are identified hallmarks of Alzheimer's brain abnormalities, which are suspected to be caused due to senile (neuritic) plaques and tangles. Plaques are formed when abnormal clusters of protein pieces called amyloid-beta ($A\beta$) clump up together between neurons. Plaques and/or tangles may destroy vital cell transport system and hinder cell-to-cell signaling at synapses. Post-mortem results of the human hippocampus, and the CA1 region in 3xTg-AD mice revealed that these alterations are administered by hippocampus^[44].

The progression of AD is studied using the patterns in which these plaques and tangles are spread through the cortex. The basis for these changes is unknown, but preferably a combination of factors commences common biochemical and physiologic pathways that finally lead to nerve cell dysfunction and death^[45]. In the *advanced stage* of AD, plaques and tangles escalate throughout the brain, and brain tissues shrivel dramatically. Patients have the highest levels of $A\beta$ peptide and neurofibrillary tangles in this stage. They become bedridden and cannot communicate, completely becoming dependent on care-takers.

ALZHEIMER'S PATHOGENECITY AND THERAPEUTIC PERSPECTIVE

1. Genetics

Apolipoprotein E4 (APOE4) genotype is the profound genetic risk factor for late-onset AD. On chromosome 19, the APOE gene has three common alleles: $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$. Apolipoprotein E (APOE) $\epsilon 4$ alleles escalate the risk for late-onset AD and mitigate the age of AD onset^[46]. Cohorts with at least one APOE $\epsilon 2$ provide some protection against AD and show better performance on neuropsychological measures as compared to those without an $\epsilon 2$ allele^[47]. On the other hand, APOE $\epsilon 3$ may play a neutral role in the disease i.e. neither increasing nor decreasing the risk^[48]. The findings of Yang *et al.*^[49] suggest that bone marrow transplants-derived APOE3-expressing cells may have better ability to reduce the behavioral and neuropathological changes in experimental AD as compared to those that express APOE4.

Sherva *et al.*^[50] reported the first genome-wide association study to investigate the rate of cognitive decline in a sample of AD subjects with longitudinal measures of cognition. Their data suggested the association of SPON1, a protein-coding gene, with the interindividual variability existing in the AD trajectories. The gene product plausibly binds to amyloid precursor protein (APP) inhibiting its cleavage by β -secretase.

Neurodegeneration and AD might be advanced by chronically elevated level of the RCAN1-1 protein^[51]. The methionine/valine polymorphism in the PRNP gene harbors the vulnerability of the disease^[52]. Tiedt *et al.*^[53] recognized a new mutation in a male patient with early onset familial AD, which resulted in the deletion of a leucine at codon 174 of PSEN1. DNA sequencing^[54] exhibited a heterozygous nucleotide transition (c.824C > T) in exon 8 of PSEN1, leading to change in alanine to valine at codon 275 (Ala275Val). Another gene family TREML2 may also foster risk alleles for AD; mainly the genes, TREML2-p.R47H and TREML2-p.S144G are associated with increased and reduced risk for AD, respectively.^[55] Coding variations in ADAM10 have also been reviewed in familial AD^[56]. A recent meta-analysis of 74,046 individuals identified 11 new susceptibility loci for AD and discussed some already known loci, which include CASS4, CELF1, FERMT2, HLA-DRB5, INPP5D, MEF2C, NME8, PTK2B, SORL1, ZCWPW1, SIC24A4, CLU, PICALM, CR1, BIN1, MS4A, ABCA7, EPHA1, and CD2AP^[57].

Green *et al.*^[58] observed the combined effects of two Alzheimer's risk alleles, APOE- $\epsilon 4$ and CLU-C, which decrease brain activity in the medial temporal lobe, a brain area affected early in AD. They used assays which are known to track an early AD intervention, executive attention assays during functional magnetic resonance imaging (fMRI) in young adults, pointing to the necessity for establishing early biomarkers of increased AD risk. The TT allele of progranulin polymorphism rs5848 is also related with increased chances of AD, suggestive of the significant role of progranulin gene in AD progression^[59,60]. Single nucleotide polymorphisms were not found to be related to AD as probed in a Polish population^[61].

2. Protein Aggregation

Aggregation of protein plays an important role in pathogenesis of most of the neurodegenerative diseases, including AD. In the process of protein aggregation^[62], a monomeric unit interacts with another monomeric unit of the same protein forming dimers, oligomers and even multimers. This is accompanied with conformational changes in the 3-D structure of the protein and formation of beta-strands. In

such a way, the size of aggregates keeps on increasing and this is normally taken care by complex cellular quality control mechanisms of the body. However, under certain adverse circumstances, like high protein concentration, complex interactions with other peptidic chains or specific cellular environment, an undesirable subset of protein may aggregate intracellularly or extracellularly^[63].

In order to stabilize the aggregated structures, the interaction between beta-strands and beta-sheets takes place, leading to extracellular precipitation of insoluble amyloid fibrils or senile plaques within beta-sheets, subsequently causing neurotoxicity^[64,65]. The formation of amyloid plaques is one of the two types of protein aggregation in the brain that characterizes AD pathology and the other is intracellular neurofibrillary tangles. Neurofibrillary tangles are composed of highly phosphorylated forms of the microtubule-associated tau protein^[66]. Tau proteins are often found in close proximity to amyloid deposits^[67,68] and have been suggested as vital mediators of amyloid plaque induced neurotoxicity.

Currently, AD is defined by the regional presence of neuritic plaques and neurofibrillary tangles in the brain along with the deposition of A β aggregation. Hence, it is justified to speculate that any kind of event that is capable of kicking off the biophysical process of tau and A β aggregation results into AD^[69]. The following topics under this section describe a number of recent studies related to the two major AD pathologies - amyloid and tau hypotheses supported with a brief framework of the biochemistry involved.

2.1 Formation of Amyloid Plaques – Amyloid Hypothesis

Long before enzymes appeared, amyloid plaques have been believed to catalyze metabolic reactions of life^[70]. Amyloid plaques are found in the extracellular region and are basically composed of a ~4 kDa protein, specifically A β protein. A β protein is the primitive component of the amyloid plaques formed in the brain tissues of AD patients^[71]. The exact mechanism of toxicity of amyloidogenic proteins is not yet known. In a recent structure-function study of amyloid pores in AD^[72], it was found that monomers adopt the U-shaped, β -strand-turn- β -strand pattern as a usual feature of beta amyloid organization.

As per in vivo and in vitro studies, A β deposits are toxic to hippocampal and cortical neurons^[64,73,74]. Amyloidogenic proteins, characterized by their ability to form fibrillar aggregates with β -sheet configurations, also play an important role in several other neurodegenerative diseases. A larger A β burden is found in the brain of living early-onset AD cohorts as compared to late-onset AD cohorts^[75], which is in agreement with those from postmortem studies. The indirect proportionality between A β burden and age-at-onset is possibly related with aging-associated decline of brain or cognitive reserve and with aging-associated increase of brain susceptibility. On the other hand, Castello and Soriano^[76] suggested that accumulation of A β is neither necessary nor sufficient to initiate pathogenesis in sporadic AD.

A β is produced by the action of two aspartyl proteases, β - and γ -secretases on amyloid precursor protein (APP)^[77-79]. Firstly, β -secretase cleaves APP to generate the N-terminal of the protein, which is then followed by the action of γ -secretases to release A β ^[80,81]. There are two basic forms of A β which depend on the number of amino acid residues produced, which is either A β 40 or A β 42. The other minor fragments of peptides, A β 37 and A β 38 have also been identified and analyzed by liquid chromatography-MS and immunochemical methods^[82].

A consistent increase in the levels of A β 42 is comparably more common than its counterpart, A β 40. A short-lived increase in the

amount of A β 42 is observed in cohorts with major head injury, a recognized AD risk factor^[83]. An elevated proportion of the 42-amino acid form is enough for progression of *early-onset* AD but this is not the case for the more common sporadic forms of AD. In autosomal-dominant familial AD, deposition of amyloidogenic protein elevates with AD-causing mutations within presenilin (PS), especially PS1 and PS2 genes and APP^[84]. Inherited mutations in PS1 and PS2 increase the ratio of A β 42 to A β 40, which leads to very early and hostile forms of AD.

The main constituents of A β plaques, A β 40 and A β 42, associate to form abnormal extracellular deposits of amorphous aggregates and aggregated forms (protofibrils and fibrils)^[85]. Fibrillary aggregates of A β may enhance the effect of oligomers and protofibrils by creating mechanical barriers for diffusion, sprouting and migration of cells in brain parenchyma^[69]. However, Walsh and Selkoe have shown that A β dimers and trimers have more neuronal toxic effect and synaptic loss as compared to fibrillary proteins^[86]. Since A β seems to be the main culprit in the AD pathology and A β oligomers are the roots of neurotoxicity in AD^[87,88], the amyloid hypothesis has become the major focus of much AD research. The amyloid pathology can be targeted either by inhibiting the enzymatic action of one of the secretases (β - and γ -secretase) or by removal of A β deposits using antibodies^[89].

The carboxyl-terminal cleavage of APP to form isoforms of A β 40 and A β 42 results from γ -secretase activity. Many potent small molecules have been developed to inhibit γ -secretase to reduce the formation of A β 40 and A β 42^[90-94], but, unfortunately, γ -secretase not only targets APP, the main precursor of A β , but also cleaves Notch receptors, which are crucially important for normal growth^[95,96]. Besides, potent γ -secretase inhibitors have several side effects like serious immunological and gastrointestinal problems^[97]. Such drawbacks have directed researchers towards the development of γ -secretase modulators^[98]. The function of these modulators is to either specifically cleave APP without affecting Notch cleavage or modify the cleavage of APP by γ -secretase to favor the production of A β 40 over that of A β 42^[99-104]. Such drugs include non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen^[34] and drugs that interact with the ATP-binding cassette of PS1 near the active site of the enzyme^[105].

The serious target-related side effects of γ -secretase have aroused interest in the possibility of targeting β -secretase for AD treatment. It is worth mentioning here that the activity of a single protease, β -secretase 1 (BACE1) is involved in β -secretase cleavage of APP^[81,106-109] and inhibition of BACE1 activity has no serious target-related issues^[110]. BACE1 inhibitors can block A β production, retard the cascade of amyloid pathology and prevent AD related memory deficits in mice brain^[111-114]. However, the struggle is still on to seek effective BACE1 inhibitors that are active in CNS. The problem lies in the large active site of BACE1, which calls for identification of large molecules as potent BACE1 inhibitors. Such heavy molecular weight molecules usually have poor blood brain permeability and are rarely stable. Some studies^[115-124] also suggest the role of BACE1 in cleavage of alternative substrates like α 2,6-sialyltransferase, interleukin-1 receptor II, P-selectin glycoprotein ligand-1, APLP2, lipoprotein and voltage-gated sodium channels, and these may play physiological roles in humans. Despite the aforementioned drawbacks to the approach of secretase inhibition, γ -secretase inhibitors, γ -secretase modulators and β -secretase inhibitors continue to actively follow as drug targets for AD therapy in the hope that the concluding benefits might outweigh the risks^[63].

The second approach to address the A β menace is to target

the degradation of the aggregated protein or the aggregates. For this purpose, immune system manipulation is the sought after therapeutic approach for AD to dramatically improve cognitive deficits and/ or reduce A β and plaque pathology. Although the desired results have been obtained on passive transfer of A β -specified antibodies in APP-transgenic mice, clinical trials on humans were stopped due to the development of sterile meningoencephalitis in a subset of individuals^[125]. However, A β immunotherapies still have hope as monoclonal A β antibodies, since the humanized monoclonal antibody, bapineuzumab ('bapi'), from the Élan-Wyeth pharmaceutical company significantly delayed cognitive decline in some cohorts^[126]. Immunotherapists also believe that the approved treatment for immune deficiencies and autoimmune disorders can be effectively used in A β clearance and cognitive improvement in AD patients^[127,128].

The intracellular A β might also play a central role in the pathophysiology of the disease. Although the A β plaques are extracellular lesions, they may mediate their toxic effects inside the neuron if soluble oligomers are the principal toxic species^[63,129]. Most of the A β is excreted from the cell through the secretory pathway. On the contrary, there are evidences that intracellular A β plays an important role in AD pathology. The disease-related isoform of A β , A β 42, appears to be more vulnerable to intracellular accumulation relative to A β 40. Intracellular A β mounts more frequently in the highly-affected region of the Alzheimer's brain, i.e. entorhinal cortex and hippocampus^[130].

The aggregation of amyloidogenic proteins damages brain mitochondria, which causes neuronal dysfunction. Mitochondrial beta-amyloid plays a critical role in the development of AD as it binds to beta-amyloid-binding alcohol dehydrogenase, a mitochondrial enzyme^[131]. It also induces oxidative stress^[132] leading to increase in the levels of lipid peroxidation products. This may trigger neurodegeneration by causing oxidative dysfunction of essential energy-related complexes in mitochondria^[133].

The intracellular A β gets bound to heme groups in mitochondrial membranes impairing electron transport chain and loss of respiratory function. The experimental affirmation of such oxidative stress leads to the basis for treatment of AD with antioxidants^[134]. Also, the profound genetic risk factor, ϵ 4 allele of APOE4, elevates intracellular A β ^[135] whereas increased synaptic activities reduce it^[136]. A β immunotherapy can be used to address the reduction of intracellular A β ^[137,138].

Also, Memantine combined with vitamin D may avert degeneration of nerve fibers triggered by A β ^[139] and can be applied to prevent the onset of AD. Memantine is accepted for treatment of moderate to severe AD. Recently, proline-rich polypeptide-1 was tested as a neuroprotective agent on A β 25-35 animal model of AD and was concluded to be one of the effective preventive agents to fight against neurodegenerative disorders^[140].

Interestingly, an executable mathematical language, Maude was used to write a computational model to simulate and logically analyze the system it models. The amyloid hypothesis was used as the basis of the AD model^[141]. On analyzing the model, it was found that A β regulation can be interrupted through the interaction of pathological processes such as cerebrovascular insufficiency, oxidative stress, and inflammation. Lately, what experiments and computer simulations can offer us about A β and its link to AD has been reviewed^[142]. In order to understand this link, the usage of computational techniques to study the A β conformational properties are encouraged, keeping in mind the challenges and limitations inherent to the current set of experimental techniques.

2.2 Formation of Neurofibrillary Tangles – Tau Hypothesis

The neurofibrillary tangles of tau protein observed in AD brains are likely to have been deposited after changes in A β metabolism and initial plaque formation^[143-145]. Discovery of tau protein goes back to some 40 years. The normal functioning of the neurons is dependent on tau protein as it stabilizes microtubules by promoting tubulins assembly. Microtubules, a major component of the neuronal cytoskeleton, is responsible for normal morphology and gives structural support to the nerve cells^[146]. Tau protein that can regulate tubulins assembly into microtubules is in the phosphorylated form. The coordinated action of kinases and phosphatases on tau protein further assists the tubulins assembly^[147-148]. Under AD pathological conditions, abnormal phosphorylation of tau protein takes place. This limits the binding capacity of tubulins to disorganize microtubules. Also, self polymerization and aggregation of tau into paired helical filaments^[149] progressively leads to formation of neurofibrillary tangles inside the neurons^[150-152]. A β -like biophysical mechanism of protein aggregation is applied for the production of tau-derived neurofibrillary changes (neuropil threads, neurofibrillary tangles, neuritic plaques). Like the toxicity of A β , toxic intermediates of tau (oligomers and fibrillary tau protein) cause toxicity at the cell biological level.

New perspectives on the role of tau in AD and its therapeutic implications have been actively pursued in a review^[153]. In AD, tau protein fails to keep the cytoskeleton well assembled in the axonal process as it fails to bind to microtubules. This abnormality is advanced by prominent modifications in the conformation of the tau native structure and tau misfoldings^[154-156]. Abnormal post-translational modifications seem to be the main reason of this abnormality^[157,158]. In Alzheimer's, fibril inclusions start from the entorhinal cortex, progressively damage the hippocampus, and ultimately the neocortex^[159]. As these regions of brain are essential for learning and memory, progression of tangles pathology is victimized with cognitive loss^[160]. The density of neurofibrillary tangles distributed along the entorhinal cortex, hippocampus and neocortex has been correlated with the degree of dementia in AD^[161].

The nonfunctionality of tau protein has been proposed to be caused due to abnormal phosphorylation, also called hyperphosphorylated state. Accumulation of post-translationally phosphorylated tau proteins takes place early in neurons, even prior to formation of neurofibrillary tangles. In the hyperphosphorylated state, the tau protein is deprived of its biological activity. In AD, the hyperphosphorylation^[162,163] might be a result of upregulation of tau kinases^[164] like GSK-3 β , cAMP-dependent protein kinase, cyclin-dependent kinase 5, and calcium/calmodulin-dependent kinase II and/or downregulation of tau phosphatases, which include PP1, PP2A, PP2B, and PP2C^[165]. It has been proposed that tau hyperphosphorylation occurs prior to its cleavage^[166,167] and formation of neurofibrillary tangles follows tau cleavage^[168]. The former has been confirmed by in vitro studies of ethanol-induced neuronal apoptosis in the developing mouse brain^[167,169]. The other proposed reasons for the loss of normal functioning of the tau protein can be acetylation, nitration, glycation, truncation, ubiquitination and conformational changes^[154,170-179].

Tau hyperphosphorylation and misfolding take place both at presynaptic and postsynaptic terminals. The abnormal post-translationally modified tau is enriched in synaptoneurosomal fractions. The accumulation of hyperphosphorylated tau oligomers at human AD synapses is associated with increased ubiquitinated substrates and proteasome components that may disrupt synapses in AD^[180]. Besides this, considerable hyperphosphorylation and

misfolding of synaptic tau take place amongst non-demented elderly, signifying synapse to be one of the first subcellular compartments affected by tauopathy^[181].

In a healthy neuron, over ten-fold excess of tau is in the microtubule bounded form^[182,183]. On the other hand, in AD affected neurons, hyperphosphorylated tau does not bind to tubulins, which leads to disintegration of microtubules. The disintegration of microtubules affects the neuronal transport system and affects the distribution of mitochondria. The disrupted distribution of mitochondria in the peripheral region of axon can decrease glucose levels, lipid metabolism and synthesis of ATP and loss of Ca²⁺ homeostasis^[184], leading to a neuronal degeneration state called “dying back” of axons. Synapses are also dependent on mitochondria for the energy required for its regular functioning^[185] and tau protein abnormalities interrupt mitochondria from providing energy to synapses causing synaptic loss^[186].

Tau proteolytic cleavage can be considered as another possible mechanism that may promote tau protein aggregation^[187-189]. Unfortunately, the enzyme that is associated with the proteolytic cleavage of tau is not clearly known. Some findings suggest association of aberrant proteolysis even with programmed cell death^[190,191]. The correlation of apoptosis and associated caspases with the neurodegenerative process in AD shows the proliferation of apoptotic cells in the protein aggregation prone areas of the brain^[192-194]. Caspases, the cysteine proteases, cleave ASP residue in the canonical consensus sequence on the carboxyl terminal of molecule. Caspase enzymes, especially caspase3, participate in a proteolytic cascade to kill cells via apoptosis^[195]. They also play a vital role in A β -induced neuronal apoptosis^[196] and are activated in apoptotic neurons in AD^[197].

Tau is also found in the cerebrospinal fluid (CSF)^[198] and increased level of tau is an AD biomarker. There are numerous pathways that have been hypothesized to explain the presence of tau in the CSF. Tau might have passively released from dead or dying tangle-bearing neurons or actively secreted and transferred between neurons through synapse^[199]. Although the intercellular transfer of tau is of great interest and vital in tau pathology, the exact mechanism of neuronal internalization of tau remains a moot question. However, it is often hypothesized that the mechanism depends upon the nature of the tau intermediate involved, say monomers^[200,201], small soluble oligomers^[202] or aggregates^[203]. In AD, the elevated levels of tau phosphorylated on T181 has been found in human CSF^[204], suggesting that tau phosphorylation may be modified extracellularly. Since it is now understood that the progression of tau pathology in AD is marked by interneuronal transfer of tau, suppressing this transfer may have an impact on AD pathology. Also, tau pathology causes synaptic loss and subsequent cell death; thus AD-related cognitive decline may be improved by preventing intercellular tau transfer. The therapeutic strategies implemented in this context are blocking tau release, reducing tau accumulation or extracellular oligomerization or preventing uptake of tau by neighboring neurons^[199].

3 Cholinergic Deficiency

Some of the demential neuropsychiatric symptoms, such as hyperactivity, depression, apathy and psychosis, may render central cholinergic deficiency syndrome^[205,206]. Cholinergic deficiency syndrome is the reduction in the synthesis of a neurotransmitter, acetylcholine^[207], which is a well-known feature associated with AD^[208]. The acetylcholinesterase enzyme is involved in the breakdown of acetylcholine by hydrolyzing it. The accessibility

of acetylcholine can be increased by using acetylcholinesterase inhibitors which inhibit the acetylcholinesterase from hydrolyzing acetylcholine. Tacrine, rivastigmine, donepezil and galantamine are the four approved acetylcholinesterase inhibitors^[209,210], but none of these can delay or halt the disease progression. In fact, for half of the AD subjects with milder forms of the disease, these drugs remained effective for just 6-12 months^[211]. Therefore, the researchers are more interested in targeting A β and tau proteins^[187,212,213] and BACE^[214].

An endogenous neurotrophic-factor protein, termed as nerve growth factor (NGF) has a potential to restore function and to avoid degenerating cholinergic neurons in AD, but offers a long-standing delivery obstacle. Recently, ten AD patients were successfully administered with genetically engineered gene-therapy vector adeno-associated virus serotype 2 delivering NGF (AAV2-NGF [CERE-110]) to the nucleus basalis of Meynert^[215]. The latter was found to be safe and well-tolerated for two years without any evidence of accelerated decline.

4. Apoptosis

For proper functioning and to maintain constant size of proliferative tissues, it is necessary for the older cells to die and make way for new cells. Apoptosis, a stereotyped sequence of biochemical and morphological changes, leads to 'programmed' cell death without adversely influencing its neighbors^[216]. Hence, it is also frequently called "programmed cell death"^[217]. In contrast to proliferative tissues, neurons of an organism need to stay alive for the whole lifetime as they are responsible for maintaining the function of cells with neuronal circuits. Unfortunately, excessive death of neurons may take place, resulting in disease or injury. For example, Alzheimer's disease involves the death of hippocampal and cortical neurons^[216].

Necrosis and apoptosis are two ways by which cell death can occur. Apoptosis is a programmed, smooth and tightly regulated physiological method required for maintaining a balance between cell division and cell death. In contrast to this, necrosis results in quick disruption of the cellular mechanism and non-physiological disintegration of the cells. A combination of both apoptosis and necrosis may occur in contributing to neurodegeneration in AD. Both may overlap or occur sequentially^[217].

Occurrence of apoptosis in Alzheimer's came into the picture in 1993 when two research teams, Carl Cotman's at the University of California, Irvine, and Gianluigi Forloni's at the Institute of Pharmacological Research in Milan, Italy, showed that A β , which accumulates in the brains of patients suffering from AD, leads to the death of cultured neurons by apoptosis^[218]. There have been many other hints regarding occurrence of apoptosis in AD^[197,219-223].

Apoptosis leads to the cleavage of the AD associated vital proteins, APP and presenilins, which are also commonly referred to as 'cell death substrates', as the process ultimately results in cell death^[224]. Presenilin mutations also disturb calcium homeostasis in the endoplasmic reticulum such that neurons are sensitized to apoptosis and excitotoxicity^[225].

Activity of the apoptosis-associated family of cysteine proteases named caspases^[226], has been found in neurons related with amyloid deposits in the brains of people suffering from AD^[216]. Gervais *et al.*^[196] suggested that APP is cleaved by caspases. They proposed that this may be an early event that facilitates the production of A β , suggesting the strong link that apoptotic cell death might have with deposition of A β . The predominant site where this proteolysis mediated by caspase occurs is within the cytoplasmic tail of APP. The cleavage occurs in hippocampal neurons *in vivo*, which

is followed by acute excitotoxic or ischemic brain. Based on sequence homology, the caspases family of proteases is classified into three subfamilies: caspase-1 (ICE), caspase-2 (ICH-1), and caspase-3 (CPP32).[226] As already mentioned, Caspase-3 shows a marked elevation in neurons that are dying in Alzheimer's disease, implying caspase-3 to be the predominant caspase involved in APP cleavage^[196]. Caspase activation is thus a prerequisite of apoptosis^[217]. Different cellular substrates for caspases have been described. For example, an essential cellular protein, ICAD, which is an inhibitor of caspase-activated deoxyribonuclease (CAD or DFF45), is cleaved by caspase, which actually begins DNA fragmentation^[227]. Caspases attack the main essential structures of the cell by cutting off contacts with surrounding cells, reorganizing cytoskeleton, shutting down replication and repair of DNA, interrupting splicing, disrupting nuclear structure and disintegrating cells into apoptotic bodies^[228]. Caspase activation may also involve signaling pathways such as apoptotic triggers like toxins, death receptors like Fas/CD95 and intracellular stress conditions^[217].

Mutations in presenilins alter γ -secretase cleavage of APP at the C terminus of A β . In one pathway, presenilin mutations increase production of A β directly, which induces apoptosis and activation of caspase. Caspase cleavage of APP further facilitates greater A β production, resulting in a vicious cycle that involves apoptosis and A β generation. In the second pathway, presenilin mutations first activate caspase which cleaves APP and results in increased A β production. Both pathways relate apoptosis and caspase activation with increased generation of A β ^[224].

Changes in expression of apoptosis-related genes like the Bcl-2 family of regulator proteins, Par-4 and DNA damage response genes and increased DNA damage have also been found to be linked to accumulation of amyloid deposits in AD brains^[216]. Bcl-2 of the Bcl-2 family of regulator proteins is anti-apoptotic, whereas some, like Bax, Bad, and Bak, are pro-apoptotic in their function. For the survival of individual neurons, balance of pro-apoptotic (Bax, Bak and Bad) and anti-apoptotic (Bcl-2 and Bcl-xL) proteins may be essential. Neurons that have high levels of Bak and Bad, and normal or low levels of Bcl-2 and Bcl-xL die, while increased levels of Bcl-2 and Bcl-xL inhibit apoptosis^[226].

Another major pathway that leads to activation of caspase is the release of cytochrome c from mitochondria. Assembly of apoptosome, a large proteinaceous complex made up of an oligomer of Apaf-1 and procaspase-9, is controlled by cytochrome c in the cytosol. When this complex is formed, caspase-9 is activated, which further activates other caspases^[229]. It lies in the space between the outer and inner membranes of mitochondria, where cytochrome c resides in healthy cells. It has been proposed that members of the Bcl2 family, such as Bad, Bak, Bax and Bid, cause cytochrome-c release^[230,231]. These proteins have been reported to form pores in the outer membrane through which diffusion of cytochrome c occurs^[232]. In fact, other apoptotic proteins and several caspases and apoptosis-inducing factor might also translocate from mitochondria to the cytosol^[229]. Apart from activating caspase and inducing apoptosis, release of cytochrome c may also result in loss of oxidative phosphorylation and production of reactive oxygen species, which may lead to cell death^[233,234].

The clarification of the mechanism of apoptosis promises to the discovery of therapeutic drugs that would help in prevention and therapy of AD^[217]. In recent years, much attention has been devoted to identify drugs that control apoptosis, but the results have been unsatisfactory. Thus, it is necessary to find novel targets for the same^[235].

5 Neuroinflammation

Inflammation or inflammatory response is an inherent part of the body's defense mechanisms to fight against numerous threats, including injuries and infections. Inflammations could be of three types: inflamm-aging, metaflammation and peripheral inflammation. Inflamm-aging is a term used to describe a condition when the immune system runs amiss with age, damaging aged tissues. Sometimes the response may be less protective and more harmful due to a low-grade and chronic form of inflammation called metaflammation. Inflammation may also exist due to damages affecting nerves, causing peripheral inflammation.

These inflammations can contribute to the AD onset by increasing the toxic levels of A β protein^[236]. It is believed to be caused by malfunctioning of blood brain barrier transporters, which then fails to push the accumulated A β proteins from the brain into the blood. These evidences suggest that proinflammatory cytokines, the cell signalling proteins which promote systematic inflammation, should be considered as therapeutic targets or relevant biomarkers in psychiatric disorders^[237,238].

Neuroinflammatory and neuroregenerative processes occur in the early stages of AD pathology^[239]. In advanced stages of AD, neocortex exhibits upregulation of inflammatory mediators. This takes place as a regenerative response to the deposition of amyloidogenic proteins. A β is considered as a foreign substance by the immunity system of the body which in turn generates anti-A β antibodies. The removal of A β by anti-A β antibodies leads to clearance of the A β deposits with subsequent reduction of the dystrophic neurites as found in transgenic APP mice.

NSAIDs tamper inflammation by inhibiting the main mediators of CNS neuroinflammation such as cyclooxygenase-mediated signaling pathways including prostaglandins. Since neuroinflammation has become an important pathological hallmark of AD, NSAIDs are associated with reduced incidence of AD^[240], but their administration has adverse cardiovascular side-effects. Thus more targeted exploitation of downstream prostaglandin signaling pathways must be addressed to prevent or therapeutically intervene AD^[241].

A two-photon excitation microscopy displays that infiltrated neutrophils in the brain migrate to brain A β plaques^[242]. The study suggests a possible influence of these immune cells on the progression of AD, especially in relation to brain inflammation. Fingolimod, a new oral immunosuppressant used to treat a neuroinflammatory disease, multiple sclerosis, may provide therapeutic effects in patients with AD, by up-regulating neuronal brain-derived neurotrophic factor^[243].

Antidiabetic drugs affect brain metabolism like neuroinflammation and neuroregeneration. This suggests the contribution of these drugs to the evolution of disease modifying treatments for neurodegenerative diseases^[236]. Ginseng Rb1 is also found to reverse the changes in a number of direct or indirect hippocampal neuroinflammation markers, indicating that this could be a potential way to develop anti-aging drugs^[244].

6 Miscellaneous

Insulin, a key factor of diabetic pathogenesis, is involved in essential pathways of learning and memory in CNS and thus contributes to the development and progression of AD in aging patients with diabetes^[245]. In early sporadic AD pathology, abnormal brain glucose metabolism and insulin signaling have been reported to play a crucial role^[246]. Over two-third of AD cohorts were clinically identified with impairment of glucose. It is hypothesized^[247] that AD, clinically and pathologically, presents a metabolic form of diabetes on the brain and

would also contribute to the pancreatic and beta-cells degeneration, leading to diabetes. Using a positron emission tomography (PET) probe of regional glucose utilization in the brain, it was suggested that severe energy deficiency for preclinical AD and MCI patients is consistent with the progression of AD^[248].

Malfunction in the iron biomineralization undertaken by ferritin may be a pivotal factor in development of AD^[249]. The amount of nanocrystals of magnetite (Fe₃O₄) intrinsically found in the human brains is generally increased in the Alzheimer's brain^[250].

Correia *et al.*^[251] carried out thorough research in autopsy brain tissues from AD cohorts, AD animals and other cellular models. They found that multiple malfunctioning takes place in mitochondria during the course of the disease. The mitochondria isolated from lymphocytes of patients with MCI have been found to undergo an increase in oxidative stress. On correlation with varying levels of a number of vitamin E components, an increase in oxidative stress markers in the peripheral system was observed^[252]. This may potentially reflect brain damage and can also serve as a potential biomarker in AD pathogenesis.

PREVENTIONS

The potential misconceptions related to risk and protective factors can be targeted with tailored educational endeavors. It was found in a study that older and middle-aged adults are concerned about their AD risk status and believe that initiatives can be taken to reduce disease risk^[253]. At present, there is no effective preventive measure for AD that comes with a definitive affirmation to support these measures. Since global studies of measures to avert the onset of AD or its delay have often produced inconsistent results, the focus has now shifted to environmental proteomics associated to the disease^[254].

1. Environmental Factors

Environmental factors such as ingestion of metals like lead^[255], iron and zinc^[256] may also be associated with the development or progression of AD. An imbalance in the levels of redox transition metals, especially iron, copper, and other trace metals has been pinpointed by current evidences^[257]. They are present at higher levels in subjects with AD and Parkinson disease while with other neurodegenerative disorders, copper, zinc, aluminum, and manganese are involved.

Aluminium is a neurotoxicant, which hastens brain aging but its extensively studied role in the etiology of AD is still debated^[258]. Some mechanisms contributing to Al-induced neurobehavioral toxicity are noted in a review^[259]. Metal ions, particularly copper(II), may contribute to the formation of amyloid plaques and neurofibrillary tangles^[260-262], which are the core pathological hallmarks of AD.

2. Diet

The role of nutrition in regulating AD is not certain, though a lower risk of AD is associated with a Mediterranean-type diet, coffee and moderate alcohol consumption^[263]. A Mediterranean diet and/or a food combination, such as Souvenaid, seem to be the most effective approaches with the least possible side effects to mitigate the progression of AD^[264]. Epidemiologically, combination supplements rich in antioxidant vitamins may also reduce the risk of AD. Retinoids, vitamin A-related compounds, reveal to be capable therapeutic targets for AD treatment because of their capability to affect the vital components of disease such as plaque formation, cholinergic transmission, APOE expressions, cholesterol content and

inflammatory environment of the brain^[265]. On the other hand, soy food consumption may lead to the increasing incidence of AD and other dementias^[266]. Additionally, vitamin D^[267] and vitamin E related compounds^[268] such as γ - and α -tocopherols are also associated with health risks.

3. Others

The risk factors of AD onset differ enormously between the sexes. Women are more prone to the development of AD than men and also more likely to be informal caregivers for someone with AD or related dementias^[15]. This entry focuses on the role of ovarian steroid hormones, especially estrogens and progesterone, and their contributions to women's neurological health^[269]. As reviewed by Li and co-workers^[270], brain estradiol, a localized female sex hormone, has emerged as a therapeutic target for preventing brain disorders and neurodegeneration. The benefits of estrogen replacement therapy for cognitive functions and AD prevention, especially in postmenopausal women, warrant attention. The biology of sex differences in cognitive function is needed to be perceived in detail to provide insight into AD prevention and development of personalized, gender-specific medicine^[271].

AD pathogenesis is associated with immoderate exposure to electromagnetic fields from electrical grids, excessive alcohol intake, hyperhomocysteinaemia, hypertension, hyperinsulinaemia and chronic anaemia^[263]. A higher risk of AD is associated with pesticides, smoking, traumatic brain injury, obesity and high cholesterol levels in middle age. Along with the well-known clinical and lifestyle risk factors, personality traits such as self-discipline and depression are also associated with AD incidence^[272].

AD BIOMARKERS

1. Current Biomarkers

Early treatment of AD patients may contribute to a small delay in their institutionalization, resulting in notable cost savings^[273]. To improve both the diagnostic and prognostic accuracy of AD and to differentiate it from other types of neurodegenerative dementia, the clinical symptoms and signs are combined with biomarkers^[274].

Throughout the review, a number of known biomarkers have already been discussed. These neurochemical indicators provide a reliable assessment of the disease and thus need a summarization. Prior to the escalation of pathological changes, they must be effectively diagnosed. Trzepacz *et al.*^[275] showed that MRI^[276] and amyloid PET neuroimaging^[277] are the best combination of biomarker modalities for predicting conversion of MCI to AD.

The definitive diagnosis of AD is only through brain biopsy or autopsy. Since CSF is in direct contact with the brain, the molecular composition of CSF can also be a useful source of information for diagnosing AD and other neurological disorders. CSF levels of A β 40, A β 42, total tau (t-tau) and phosphorylated tau (p-tau) usually form a part of the clinician's tool for accurate AD diagnosis. Soluble A β oligomers are also one of the diagnostic tools, as they are more synaptotoxic for AD relative to A β aggregates. Gene mutation in presenilins and APP is a genetic predisposition to early-onset AD and can be a good predictor of the same.

Different phosphorylation epitopes, mainly tau181, can be detected by different immunochemical methods. MCI to AD transition can be distinguished from stable MCI with 90% and 100% sensitivity and selectivity respectively, with the help of t-tau. On the other hand, p-tau181 shows a 80% sensitivity and 92% specificity to discriminate AD from healthy cohorts^[278]. Thus, p-tau reveals a higher specificity

than t-tau for diagnosing AD as compared to other types of dementia. Also, several kinases and phosphatases, especially cdk5 and Gsk3 β , involved in the hyperphosphorylation modifications, characterize AD.

Upregulation of the brain's innate immune response is another prime marker for neuronal degeneration in AD, which results in inflammatory processes. Besides CSF, amyloid and tau pathologies are ubiquitous in blood, saliva, skin and extra brain tissues, and have moderately promising diagnostic values^[278]. Now, let us discuss certain new potential biomarkers that have emerged to predict the risk of AD progression.

2 New Potential Biomarkers

The typical findings of established and new MRI procedures in healthy aging, MCI, and AD are well documented^[279-281]. Increased cortical phase shift in AD patients demonstrated on 7-tesla T2*-weighted MRI is a contemporary biomarker for AD, which may manifest amyloidogenesis in the early stages^[282]. Using multitask learning algorithms, Zhou *et al.*^[283] analyzed MRI and cerebrospinal fluid data of the temporal patterns of biomarkers in disease progression. They found that cortical thickness average of left middle temporal, left and right entorhinal, and white matter volume of left hippocampus play crucial role in predicting Alzheimer's disease Assessment Scale cognitive subscale (ADAS-Cog) at any stage of the disease progression. ADAS-Cog^[284] is one of the cognitive measures designed for clinical evaluation of cognitive status of the AD patients.

Welling *et al.*^[285] postulated that antimicrobial peptides (AMPs) may be labeled as a marker to target pathogens that play a role in aggregation of A β in the brain. AMPs can effectively penetrate infected cells and tissues beyond many endothelial barriers, including blood brain barrier. So, cerebral infections caused by environment influences such as viral or chronic bacterial infections can be detected and diagnosed by AMPs.

Badía and co-workers^[286] took the challenge to find the biomarkers of early-onset familial AD, a boon to young healthy individuals at risk of AD. Alzheimer's has been associated with oxidative stress. Lymphocytes from young, healthy persons carrying at least one APOE ϵ 4 allele, the strongest known single genetic risk factor for AD, were considered. It was found that lymphocytes suffered from reductive stress rather than oxidative, i.e., lower oxidized glutathione and P-p38 levels and higher expression of enzymes involved in antioxidant mechanism, such as glutamylcysteinyl ligase and glutathione peroxidase. On the other hand, in the full fledged AD, the antioxidant mechanism probably gets exhausted, the situation is reversed and oxidative stress occurs. The findings of Badías' group provided an insight into the early events of AD progression that may help to find biomarkers of Alzheimer's at its very early stages.

The largest multiplexed plasma protein study till date for AD markers describes some novel protein associations, and also validates some previously identified ones^[287]. Prostate-specific antigen complexed to α 1-antichymotrypsin, pancreatic prohormone, clusterin, and fetuin B were found to be the strongest association of protein levels with AD. Their findings provide strong affirmation that quantities of these plasma proteins are truly associated with AD.

MicroRNAs (miRNAs), endogenous small RNAs of 21–25 nucleotides, post-transcriptionally regulate gene expressions. Recently, circulating miRNAs have been reported as potential new biomarkers for neurodegenerative diseases and processes affecting the central nervous system^[288]. The study was carried out to investigate the potential role of serum miRNAs as diagnostic biomarkers for AD. Their results indicated that serum miR-125b may act as a fruitful

noninvasive biomarker for AD. Due to the easy availability of blood serum from AD patients, the phospholipid alterations occurring in serum can be investigated as promising biomarkers for diagnosis of AD^[289]. These alterations are indicative of membrane breakdown processes in pathogenesis of AD.

Labeling tissue transglutaminase (tTG) as a biochemical marker for AD can be misleading^[290]. In another report^[291], the results of Wolff and co-workers were criticized on the basis of the experimental conditions taken into account by them and the overwhelming evidence in the literature which reports tTG to be a promising biochemical marker of AD. Extracellular vesicles may also play a role in initiation and progression of AD. Both normal and pathological cells release extracellular vesicles which help in getting rid of unwanted cellular substances. These vesicles are even functional in intercellular communication like exchange of messenger RNAs, noncoding RNAs, and proteins between healthy and/or pathological cells^[292]. Perceiving the significance of the role played by extracellular vesicles in AD initiation and progression, may help in the discovery of new potential biomarkers.

A novel concept of specific immune-sensing application on the controlled silanized surface was proposed to quantify the biomarkers of AD in biological fluids^[293]. The method employed grafting of the antibodies involved in the detection of AD biomarkers over the silanized surface followed by evaluation of biological activity using fluorescence microscopy. Machine learning methodologies are also used to predict cognitive and disease states from neuroimaging data^[294]. The progression of disease associated with aging, such as AD, is characterized by gradual and continuous changes in the shape of the brain.

Most of the contemporary shape analysis studies in AD and related dementia perform statistics on the specific region of interests, already clinically known to be affected. Recently, a multivariate analysis of diffeomorphic transformations of the whole brain was presented^[295]. The complex anatomical changes were related with neuropsychological responses, such as clinical measures of cognitive abilities, logical memory, audio-verbal learning, and measures of executive functions. The proposed methodology may discover new patterns of shape changes in the human brain that can help in envisaging progress of disease in neurological disorders.

CONCLUSIONS

Unfortunately, the damages caused to the brain cannot be reversed with ongoing treatments and the disease is incurable. At this time, there is no treatment to slow down the rate of progression of the disease. So, it was necessary to have new insights into the pathophysiology of AD. Courageous efforts, cooperation and endurable management are needed to perceive the incredibly complex AD, as aging population forms an important part of our society. With increase in the lifespan, the number of patients with cognitive diseases is only going to increase, and unless steps are taken right now to slow down the progress of age-related diseases, AD may take on epidemic proportions.

CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

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