Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-149-7_1

Chapter 1: Understanding Alzheimer's Disease Pathophysiology and Therapeutic Gaps

Sagarika Mukherjee[1], Parikshit Roychowdhury[2], Subhajit Dutta[3], Gobinath Manavalan[4], Nivedhitha S[5], Mirunalini Gobinath[1*]

[1]*Department of Pharmacognosy & Phytopharmacy, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty-643001, Tamil Nadu, India.*
[2]*Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty-643001, Tamil Nadu, India.*
[3]*TIFAC CORE HD, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty-643001, Tamil Nadu, India.*
[4]*Department of Pharmaceutical Chemistry, Swathi College of Pharmacy, Venkatachalam, Nellore, Andhra Pradesh, India.*
[5]*Department of Pharmacognosy, Swathi College of Pharmacy, Venkatachalam, Nellore, Andhra Pradesh, India.*
Corresponding Author
Dr. Mirunalini Gobinath
Email: mirunalinigobinath@gmail.com

Abstract

Among all the neurodegenerative disorders, Alzheimer's disease, which is the common cause of dementia, is the leading disease that is being seen as the burden in healthcare sectors, affecting economics and health of the public. This disease is caused due to two pathways, firstly being the extracellular beta amyloid plaques and secondly the intracellular tau containing neurofibrillary tangles. In the recent years, there were countless development that involved underlying mechanisms, genetic modifications that includes curative or protective genes, and the change in the lifestyle that can be effective for Alzheimer's disease. A rough estimation has been made by Alzheimer's disease international that states that there will be numerous cases approximately, 55 million people will be affected by dementia associated with Alzheimer 's disease. And this can increase thrice the present estimation by the end of this century. The advanced age and alleles APOE ε4 are the leading factors that causes AD. Between males and females, the higher risk of succumbing to AD are in females rather than in males. Hereditary is the root cause of around 80% of the cases. The risk increases with the presence of variants like PSEN2, APP, SORL1, etc. Whereas variant genes like APP673T, APOE e2, etc. are protective in nature. This chapter deals with pathophysiology, genetic variations, any other alterations that gives access to the formation of amyloid plaques and tau containing neurofibrillary tangles.

Keywords: *Neurodegeneration; Pathogenesis; Amyloid plaques; Cellular senescence; Oxidative stress; Mitochondrial dysfunction*

1. Introduction

Alzheimer's disease is a type of neurodegenerative disorder, caused by dementia. It is generally seen in geriatric patients. The specific characteristics of this disease is due to the abnormal protein deposition and aggregation that leads to the formation of plaques, generally the extracellular beta amyloid plaques, and tangles containing the intracellular tau containing neurofibrillary tangles, that gives rise to the disruption of the function of the neuron and eventually leading to cellular death (1). Clinically AD is presented in 2 types, namely, typical, where prominent amnestic cognitive impairment which focusses on short term memory loss; and, atypical where there is difficulty in speech expression, deficiency in visuospatial processing and executive function impairment which is nothing but the mental agility. The less common clinical presentation is non amnestic variants (2). The first reported condition of AD was done by a German psychiatrist and neuroanatomist, Alois Alzheimer, who described it as a disease that affect cerebral cortex that involves in cognitive and memory losses (3).

After scrutinized research, AD is now recognized as a form of dementia. It is a neurodegenerative disease that forms degeneration of neurons in the brain and its parts, especially cerebral cortex. The cerebral cortex which is a well-developed part of the brain that is important for functions like cognitive learning, perception, decision making, memory conceptual thinking, awareness etc and initiates motor functions. (4). The cognitive impairment is a spectrum of subjective cognitive decline which is the early stage of AD, followed by mild cognitive impairment where one or more cognitive areas show impairment, but functional independence remain intact. The last stage is the dementia where there is gradual onset including prominent memory loss which is classic AD Phenotype. The progressive impairment is sufficient to disrupt independence and daily life, which is generally characterized by the buildup of the plaques of the extracellular beta-amyloid, and aggregation of the intracellular neurofibrillary tangles (5).

Initially, AD is manifested by early signs of amnestic cognitive impairment along with short term memory difficulties. With its progression, AD affected patients may have experiences associated with impairment of complex attention, visuospatial processing, executive functions and expressive speech (6). The symptoms of neuro-psychiatric nature often get accompanied by deficient cognitive behaviour in AD, especially, during earlier stages, when there is prevalence of apathy, depression and anxiety. As the disease starts to progress, the patients affected with AD, may have development of additional symptoms of agitation, aggression, delusions, hallucinations, irritability and lability (7). Clifford Jack et al., with the advanced knowledge and technology in research of biomarkers, re-named the diagnosis of AD, and, transformed purely clinical syndrome to a biological framework depending on the biomarkers. These

biomarkers are categorized as β-amyloid deposition, Pathological tau protein, and neurodegenerative biomarkers (8).

In the year 2010, the above-mentioned researchers, Jack et al., gave a hypothetical model related to dynamic biomarkers for AD, which spanned the cognitive continuum to dementia from health (9). They divided the disease into three phases, namely pre-symptomatic phase, prodromal phase which is often known as MCI (Mild Cognitive Impairment), and dementia phase. Occurrence of AD in predisposed patients via beta amyloid pathology, is around 15 to 20 years before the onset of progressive cognitive decline is anticipated (10,11). With the elevation of CSF, levels of tau, show indications of neuronal injury and severity of the disease correlation. PET using fluorodeoxyglucose, has been a remarkable marker for dysfunction of the synapses which are associated with neurodegeneration in patients contracting AD (10). Figure 1.1 represents the pathological difference between normal brain and Alzheimer's brain.

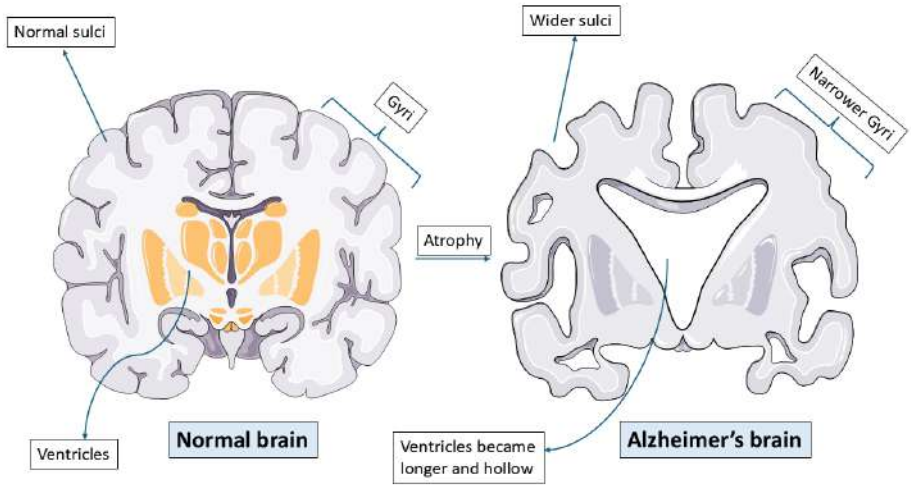

Figure 1.1 Normal brain Vs Alzheimer's brain, undergoing atrophy

2. Epidemiology

Dementia results from two causes, first neurodegenerative diseases like frontotemporal dementia and second one being cerebrovascular pathologies like strokes. In some individuals, especially geriatric patients, have multiple overlapping pathologies. In one neuropathological study concluded the following 31% have suffered from only AD pathology, 22% contracted AD with alpha synuclein pathology generally associated with Lewy bodies, 29.5% had AD with TDP43 pathology often seen in hippocampal inclusions and 17.5% suffered from AD and alpha synuclein and TCP43 pathology known as triple pathology, along with 29-52% had cerebral infarcts like microinfarcts,

lacunar infarcts as well. The global prevalence growth estimates that dementia cases are expected to more than double from 50 million in 2020 to 113 million by 2050(12).

Around 1% of AD cases, come under the "early-onset autosomal dominant AD" category. This category of AD gets manifested, typically, before 65 years of age where people within the ages of 40s and 50s start experiencing the symptoms. Whereas the rest 99% fall into the "late-onset sporadic AD" category (13). Then, there are genetic predispositions that significantly influence the mechanisms of pathophysiology of AD, which accounts for the 58 to 79 percent cases on estimation. Mutations which are rare, especially in, PSEN1, PSEN2 and APP are often related to the autosomal-dominant AD type (14). The gene, Apolipoprotein E (APOE), is mostly, one of the main genetic risk factors for Sporadic dominant AD type. APOEε4 prevalence is seen to be 66% among patients with dementia of AD-type and 64% among patients suffer from MCI. If there is one APOEε4 allele in possession, it amplifies the risk of contracting AD rises to 3 to 4 folds. But if a patient possesses 2 of such alleles the risk further elevates up to 9 to 15 folds (15).

There have been studies done regarding whole genome sequencing and genome wide association studies, which has revealed that there has been an additional genetic locus associated with the risk of AD having late onset, which includes ABCA7, BIN1, CD2AP, CD33, CR1, EXOC3L2, BLOC1S3, MARK4, PICALM, MS4A6A, MS4A4E, TREM2 out of all (16). There was a meta-analysis done that helped to further identify several other susceptibility loci for the late onset AD, inclusive of DSG2, CELF1, CASS4, FERMT2, HLA-DRB5, HLA-DRB1, PTK2B, SORL1, SLC24A4, RIN3, INPP5D, MEF2C, NME8, ZCWPW1(17).

During a study in the US, around 21.1% of women and in men, around 11.6%, whose age is over 65 years are AD patients. There have been 12 modifiable risk factors that were identified, by the Lancet Commission on Dementia Prevention, that are said to be collectively accountable for somewhat 40% of the dementia cases worldwide. These factors are inclusive of, depression, diabetes, hypertension, hearing impairment, limited social interaction and lower education levels (18).

3. Risk Factors

For Alzheimer's to be progressive, the main risk factor is the advanced age which is the geriatric patients with age ranging from 60 – 65 years and above. Following the advanced age as the risk factor, another factor that is risky is APOE ε4 alleles. Another factor that is placed in this parameter is the gender of the patients. It is seen that female geriatric patients are more prone to Alzheimer's than men (19). The β-amyloid load has been seen to be similar. The only change or difference seen is in tau entangles and load is more prominent in females than in men, which is why women are more prone to AD. Apart from the above main risk factors, there are various other reasons for a

patient to be AD prone. They are unhealthy lifestyle, CDV risks which are observed during the onset of dementia. These risk factors are seen to account up to 40% of the dementia cases. In the recent rigorous studies, it is seen that cerebrospinal fluid biomarkers states that despite these types of factors do induce dementia but does not follow by AD pathway (5,20).

In one research done, it is said that CVDs and AD are interconnected with each other via number of biological mechanisms for instances like oxidative stress, inflammation, disruption of the blood brain barrier and endothelial dysfunction. The chronic HTN and hypercholesterolemia further leads to endothelial dysfunction, which has seen to share with the increased levels of beta-amyloid and tau proteins which are the key biomarkers of AD. Amyloidogenesis and tau hyperphosphorylation are promoted via the contribution of oxidative stress and inflammation in CVDs by vascular damage, atherosclerosis and impaired nitric oxide signalling (21).

3.1 Genetic risk factors

a) APOE

This gene is in the humans, on the chromosome number 19. It is characterised by 3 forms of allele APOEε2, APOEε3, and APOEε4. The distinguishable differences among these variants are the amino acid positions in 112 and 158. Especially, APOE2 has cysteine at both 112 and 158 positions. APOE3 carries cysteine at 112 position and 158 position is occupied by arginine. APOE4 carries arginine at both the positions mentioned above, that is, 112 and 158. The above mentioned, variations in the positions of the amino acids, have a significant influence in the structure and function of the APOE, which affects the ability of it, to bind to receptors and lipids (22).

It plays a very critical role, in the transportation of cholesterol and other lipids into the neuronal cells, via their interaction within the receptors present in the cell surface, like LDLR and its related protein 1, LRP1. APOE4 is often linked to the increased risk of AD via mechanism such as aggregation of beta amyloid enhancement, amyloid plaque formation, CAA pathology, early beta amyloid seeding and intraneuronal beta amyloid accumulation (23). In comparison with them, APOE2, has been observed to show, that it protects against the beta amyloid pathology progression over the time (24).

APOE4 is said to worsen the pathology of tau, inflammations in the neurons and atrophy in the brain, in the APOE4- targeted replacements PS19 mice as compared to variants, APOE2 and APOE3(25). Moreover, APOE4 is expressed via microglia, disrupting the lipid metabolism, impairing microglial function and reduces the microglial ability to respond to pathology to AD. Likewise, the expression of microglia of APOE3 is linked with increased proximity of the microglia to amyloid plaques, there

is a decline in in amyloid pathology, therefore, there is an improvement in the cognitive function(26).

b) TREM2

Gene, known as triggering receptor, expressed on myeloid cells 2, shortly, known as TREM2, in humans, is in the chromosome number 6. It is expressed exclusively in the microglia within the central nervous system. This gene is a single transmembrane immune receptor of the immunoglobulin superfamily. The heterozygous variant TREM2-R47H, shows significant elevation in the risk of AD by 3 to 4 folds (27). The transmembrane helix, which is located within TREM2 interacts with the DAP12 adaptor protein, is very crucial for TREM2 membrane to stabilize and to initiate the downstream signalling pathways. The variants that link to AD gets to affect the TREM2 expression, into the cell surface trafficking, its ligand binding, its shedding, and including its downstream signalling (28).

TREM2 deficiency causes an exacerbation in tau pathology within a humanized tau mouse model. While haploinsufficiency of TREM2 causes intense tau pathology and brain atrophy in PS19 mice. Whereas TREM2 complete deficiency, protects against microglial activation which is tau-mediated and brain atrophy. Even though some researchers have reported that there is no effect of deficiency of TREM2 on tau pathology in PS19 mice (29).

c) Trisomy21

The most frequent kind of intellectual disability is Down syndrome (DS), caused by chromosome 21 triplication. Globally, DS affects about one in every 1000 infants, with an estimated 5.4 million people living with the condition. Trisomy 21 is the most significant risk factor for early-onset Alzheimer's disease, as all individuals with DS show neuropathological symptoms by the age of 40. Research suggests that individuals with DS have higher amounts of Aβ and tau proteins, both linked to Alzheimer's disease, as they age (30).

3.2 Other risk factors

a) Aging

Aging is the primary risk factor for sporadic Alzheimer's disease. As organisms age, DNA damage accumulates, leading to more senescent cells. Senescence-associated secretory phenotype (SASP) occurs when cells secrete proinflammatory cytokines, which can lead to age-related disorders (31). The accumulation of somatic mutations in neurons throughout aging and Alzheimer's disease is attributed to increased oxidative damage. High amounts of DNA double-strand breaks have been associated to structural abnormalities and disturbances in the 3D genome (32). A study found that combining heterochronic parabiosis with intravenous injections of young mouse plasma improved

working and associative memory in APP-transgenic mice. However, this did not affect amyloid plaque levels (24).

b) Environmental factors

In 2016, herpes simplex virus type 1 (HSV1) was expected to affect 3.752 billion persons 66.6% of the global population under 49. Autopsy examinations of AD cases have found HSV1 DNA in the brain. HSV1 infection has been related to an increased risk of Alzheimer's disease, particularly in persons carrying the APOEε4 genotype (33).

HSV1 infection significantly increased Aβ plaque development in 5 times FAD mice and a 3D human brain cell model (34). Research suggests that taking anti-herpetic drugs can reduce the incidence of dementia in HSV-infected people, while the herpes zoster vaccination can also protect against dementia (35) HIV-associated neurocognitive dysfunction (HAND) affects 20%-60% of people with the virus and HIV-infected people's brains contain amyloid plaques. Human cytomegalovirus (CMV) infection has been linked to a 2.15-fold increased chance of acquiring Alzheimer's disease. Murine CMV infection has been linked to accelerated tau pathology in mouse fibroblasts and rat primary neurons (36).

Three bacterial species have been identified: Borrelia burgdorferi, Chlamydia pneumoniae, and Porphyromonas gingivalis have been implicated in the brains of Alzheimer's patients. Research suggests that persons with Alzheimer's disease had higher levels of Helicobacter pylori in their gastrointestinal mucous membrane, serum, and plasma (37). Itzhaki et al. (2020) argue that the significance of infections in the aetiology of Alzheimer's disease is still under question (38).

c) Lifestyle Habits

Sleep disturbances are associated with an increased risk of Alzheimer's disease. Research shows that disorders including obstructive sleep apnoea (OSA). Insufficient sleep duration is linked to a higher risk of cognitive impairment. High sleep fragmentation, rather than short sleep duration, has been linked to memory deterioration and cognitive impairment in people aged 30-40 years over a decade (39). Sleep disturbances and irregular circadian rhythms are widespread in the years leading up to Alzheimer's disease, even before symptoms appear. Sleep deprivation disrupts molecular clearance systems in the brain and disrupts sleep patterns, particularly deep (slow) sleep (40).

Studies have connected wave sleep to higher levels of Aβ and tau in the brain. Sleep deprivation led to more Aβ deposition and tau pathology in APP/PS1 transgenic mice with the APOEε4 genotype, but not in those with the APOEε3 allele. Xie et al. (2013) found that natural sleep or anaesthesia improves CSF-ISF exchange and promotes Aβ elimination. T2DM, characterized by hyperglycaemia, insulin resistance, and peripheral inflammation, is linked to an elevated risk of Alzheimer's disease (AD) (41).

T2DM is linked to cerebrovascular illness and cognitive abnormalities. Aβ and hyperphosphorylated tau have been discovered in the pancreas of T2DM patients. Research indicates that Alzheimer's disease is classified as "type 3 diabetes" due to its association with glucose hypometabolism, insulin resistance, and decreased insulin-like growth factor signalling (42).

HFD-induced insulin resistance has been linked to increased Aβ production, amyloid plaque deposition, and cognitive impairment in transgenic AD mice. One study found that HFD feeding resulted to microglial activation and cognitive deficits in both wild-type and 3× Tg AD mice but did not impact Aβ or tau pathology (43). Early HFD feeding before severe AD pathology was found to prevent Aβ plaque deposition and improve cognitive performance in Tg6799 AD mice. High salt intake (≥12 g/d) has been linked to a 330% increase in cognitive impairment in older persons. A high-salt diet (HSD). In mice, cerebral endothelial dysfunction and decreased blood flow along the gut-brain axis caused cognitive impairment. HSD consumption activated calpain and CDK5, leading to tau hyperphosphorylation and cognitive impairment in both wild-type and rTg4510 mice. However, it had no effect on Aβ levels in Tg2576 mice (44). A high consumption of vitamins C and E has been linked to a lower incidence of Alzheimer's disease, probably due to antioxidants that reduce neuronal death by preventing oxidative damage (45).

d) Cardiovascular and cerebrovascular disease

Cardiovascular disease (CVD) is the main cause of illness and mortality among older persons, highlighting its significant public health effect. A growing body of research suggests that having CVD, particularly vascular dementia, increases the likelihood of getting dementia. CVD risk factors include high blood pressure, dyslipidaemia, obesity, and diabetes, which have been extensively reported in the literature (46). Research indicates that heart failure increases the risk of Alzheimer's disease by 1.8 times. Additionally, hypertension medications show promise in reducing dementia risk. Additionally, a low diastolic pressure (less than 70 mm Hg). This raises the likelihood of getting dementia. Cerebral hypoperfusion is a typical early anomaly seen in both Alzheimer's disease and vascular dementia. Midlife cardiovascular risk profiles are linked to lower brain perfusion later in life, emphasizing the need of maintaining cardiovascular health throughout life. Maintaining cardiovascular health reduces the incidence of dementia and slows cognitive decline (47).

Autopsy samples from up to 75% of persons with AD show contemporaneous cerebral vascular pathology, indicating a large overlap between AD and vascular disease conditions. Researchers found a substantial link between severe cerebral atherosclerosis or arteriosclerotic neuropathology and an elevated risk of Alzheimer's disease. Cerebral infarctions have been linked to increased risk of cognitive impairment and Alzheimer's dementia, highlighting the link between cerebrovascular health and cognitive

performance. CAA is a common cerebrovascular disorder characterized by Aβ accumulation in vessel walls. CAA often co-occurs with AD pathology in aged brains, hastening the progression to AD dementia (48).

Over 70% of people over 50 have indications of cerebral small vessel disease (CSVD), which can cause acute strokes and MCI. Dementia can result from chronic injury, tiny vessel blockage or leakage, blood-brain barrier collapse, and cerebral blood flow deficits. Neurovascular impairment exacerbates Aβ and tau pathology, leading to cognitive deterioration. CSVD is a common cause of vascular dementia that often coexists with Alzheimer's disease, illustrating the complicated relationship between vascular and neurodegenerative processes in cognitive impairment (49).

e) Traumatic Brain injury

Research suggests that TBI increases the likelihood of acquiring Alzheimer's disease at a younger age. Postmortem investigations have shown Aβ plaque buildup in roughly one-third of TBI patients. Studies on 5× FAD transgenic mice indicate that mild TBI can exacerbate BBB leakage, Aβ plaque formation, and cognitive deficits. Tau protein levels in CSF and peripheral blood increase after TBI, suggesting accelerated tau pathology. Repetitive mild TBI can lead to chronic traumatic encephalopathy (CTE), which is a progressive tauopathy without amyloid pathology (50).

4. Pathophysiological Mechanisms:

a) Amyloid burden

The Golgi and endoplasmic reticular systems of neuronal cells, play a role in the secretion and production of beta amyloid. Enzymes like β and γ secretases act predominantly in the pathological secretion of beta amyloid. The secretary pathway directly proportional to the above-mentioned enzymes. Amyloid precursor protein also known as APP, a protein, is a precursor for the synthesis. In the cell membrane, APP migrates, and in this cell membrane itself gets broken into two parts via enzyme alpha-secretase. The two parts are soluble, namely, APP-alpha or sAPP-alpha and the second being C83 APP which constitutes about 83 fragments of amino acids. APP-alpha gets released in the extracellular matrix, where the APP which is intact and are still present are generally taken up by the cells by internalization via endosome formation. An enzyme, SORL 1, is said to be involved in the recyclization of the unused APP to the Golgi complex. APP gets engulfed via endosomes that contain APP-cleaving beta-site enzyme I also abbreviated as BACE1(51).

This happens in the optimal pH inside the endosome where the above-mentioned enzyme incises the APP into fragments of 99 which is termed as C99, which migrates into the cell-membrane. It can also be transported and retraced back to ER. And within the ER it is further processed to again form beta- amyloid by the ER gamma- secretase. This gamma- secretase is found in the cell membrane where the former fraction is

migrated. Then the beta-amyloid which got released during the process, in the extracellular matrix is also gets swamped by the cells by creating primary endosomes via the action taking place in the various receptors present for example alpha-7nAChR or alpha-nicotinic acetylcholine receptors, FMLP or FPRL1 receptors that are protein in nature, LDL related protein receptors (LRP), NMDA (N- methyl-D- aspartate), and advanced glycation and product receptors (RAGE) (52).

The amyloid burden determines the pathophysiology of Alzheimer's disease repeatedly. (53). There is a confirmation of the fact of the amyloidogenic beta- amyloid build-up. And the deposition that happens in the brain is the critical factor in AD development (54). It concludes one thing that identification of pathogenic mutation in the APP gene has resulted in the brain precipitations formation which are insoluble beta-amyloid in the formation of plaques in Alzheimer's affected brain. APP is often associated with cell growth, ion transportation, neurite growth function, maintenance of synapses, physiologically. Generally, during the conditions of non-pathological nature, APP is processed and cut into innocuous fragments (55). Nonetheless APP that is mutated undergoes processed in presence of beta and gamma secretase to produce beta-amyloid peptides which majority of beta-amyloid. Then these peptides get aggregated into toxic forms like fibrils, oligomers, protofibrils, due to the mutation that takes place. The damage occurs in the neuronal membranes due to these toxic aggregates. And this damage causes neurons to die, synaptic system failure and loss of memory subsequently. There is a study that shows that beta-amyloid oligomers have interrupted the transmission of synapses and memory, empirically. In this regard, beta-amyloid, is seen to be the specific biomarkers for the neurodegenerative disorder. Indication of different progressive stages of AD depends on the concentration of the Amyloid. The species of amyloid beta aggregation, specifically blocks AMPA and NMDA receptors which gives rise to impairment of memory and cognitive dysfunctions (56). The other pathological processes also include the inflammation and oxidative stress contribute to amyloid load, giving green signal to critical therapeutic target for AD pathology modification (57).

AD is a disorder characterized by synaptic impairment. It is a synaptic failure disease that affects brain circuitry at the molecular, cellular, and macroscale levels, with a focus on the cognitively eloquent cortex, which is crucial for memory, language, and executive functions. This explains genetic results, cellular abnormalities, neuropathological patterns, and clinical symptoms such as disorientation. There are two categories of problematic features: Positive pathologies include tau-containing neurofibrillary tangles, αβ containing amyloid plaques, activated glial cells, and expanded endosomes, all of which indicate early synaptic impairment (58). Negative pathologies involve loss or dysfunction rather than accumulation, such as synaptic homeostasis, neuronal death, and disruption of neural networks and connectivity. The amyloid cascade hypothesis (amyloid accumulation leads to tau disease, synaptic failure,

and dementia) has long been prominent. However, it does not explain all disease mechanisms and underrepresents hidden, non-amyloid/tau processes. The new perspective stresses network fragmentation, immunological responses, lysosomal and metabolic abnormalities (59). Figure 1.2 shows a detailed description of amyloid burden in the pathogenesis of AD.

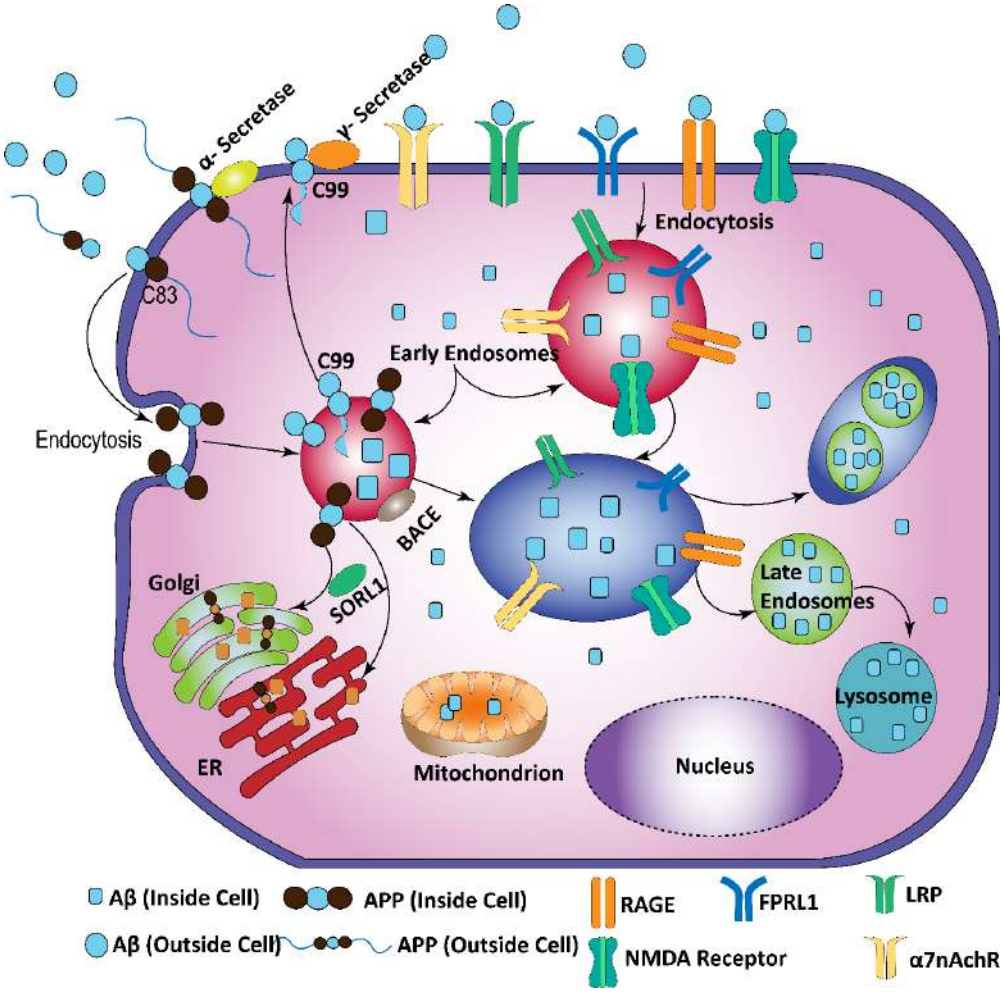

Figure 1.2 Amyloid plaques burden in the pathogenesis of AD

b) Tau toxicity

Protein that are associated with microtubules stabilize those microtubules in the neurons which includes tau. The tubulin with the interaction of tau promotes assembling microtubules which are regulated by phosphorylation. Tau that are hyperphosphorylated are called p-Tau. They impede the tau that have normal function. AD and tauopathies are diseases that occur due to this hyperphosphorylation of p-Tau. Aggregated p-Tau, forms PHFs and NFTs that impairs the axonal function. This results in degeneration of neurons (60). Beta-amyloid, by itself, directly can stimulate the glycogen synthase kinase which causes tau hyperphosphorylation. This would cause a direct link between amyloid hypotheses and tau. Tau that are misfolded spreads between neurons in amyloid load dependent way. There is an exacerbation of pTau accumulation by APOE4, due to the impeding of their clearance (61). Figure 1.3 describes the role of tau phosphorylation in the pathogenesis of AD.

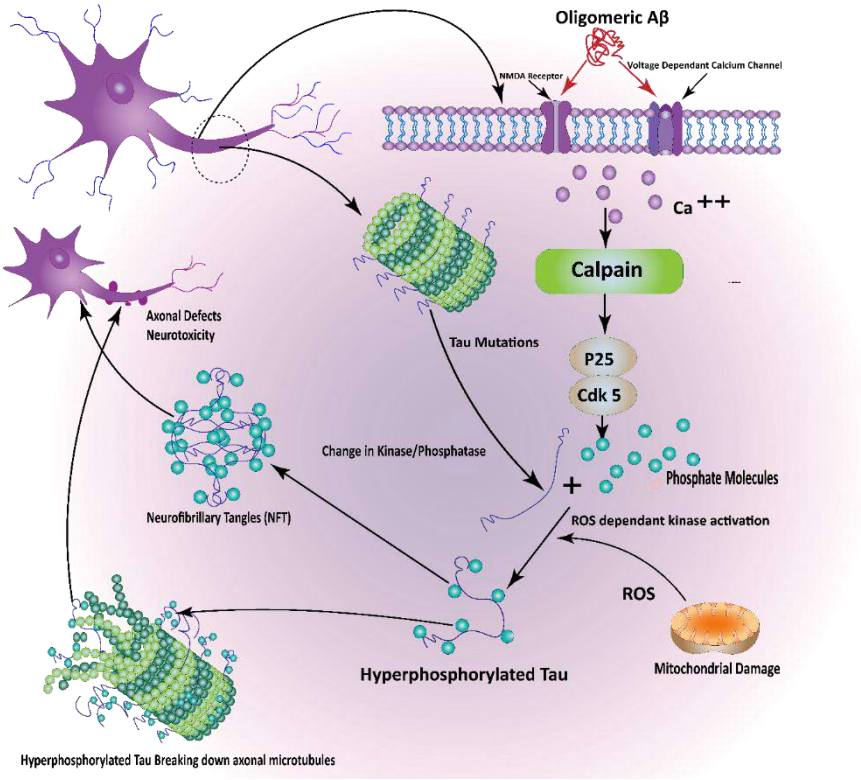

Figure 1.3 Tau hypothesis in pathogenesis of AD

c) Damage due to metal and biomolecule

Metal ions are the essential part of biological process. And AD is sometimes associated with the imbalance of these metal ions. Iron, Zinc and Calcium are the most prevalent ions in the CNS. And these are important for both function of the neurons and enzyme activity (62). Although, accumulation of excess metal ions, causes formation of

complexes with the aggregates of amyloids, because of which Alzheimer's Disease pathology gets exacerbated. With zinc ions and calcium ions there is induction of amyloid aggregation. And the increase in iron concentration which are observed in the beta-amyloid depositions causes induction of iron driven cell death which is termed as ferroptosis. In AD implications of aluminium ions also has been observed (63). Calcium ions and iron ions which are redox active metal ions, they stabilize the toxic oligomers of beta- amyloid which are responsible for dysfunctions in terms of cognitive and synaptic. The complexes of beta-amyloid and metal generate reactive species. These may cause neuronal inflammation and oxidative stress (64). Metal ions of biological nature, affects the synthesis further and APP processing is also affected. Therefore, this results in an enhanced production of beta-amyloid pathologically. Chelators with metal origin neutralizes beta amyloid that are bound to metal ions. Agents of multifunction nature targets various Alzheimer's disease related toxicities that represents promising strategies for therapy (65). In neurons, RIS balancing is most important. This is done to cause deviation from normal RIS levels. Doing so will provide oxidative stress to damage the mitochondrial and nuclear DNA with proteins and lipids. By oxidation, PUFAs are attacked easily so as to deliver by-products that are neurotoxic to AD (66). Due to the resultant oxidative stress, enzymes contribute to the damage in molecular level that are associated with the mitochondria of the neuronal cells in AD (67). The damage of the mitochondrial DNA is essentially induced by the oxidative stress. This results in the damage of the 8-oxoG marker in neurons affected with Alzheimer's (68). Neurodegeneration, is led by the overall damage in the neuronal cells, caused by oxidative stress, disrupting their physiological functions (69).

d) Oxidative stress and mitochondrial dysfunction

Reactive nitrogen species termed as RNS and reactive oxygen species termed as ROS are essential in cell signalling and the defence against infections by the host. And oxidative stress is caused due to their overproduction (70). Damage that occurred due to DNA, proteins and lipids due to oxidative stress causes neuronal death. These types of oxidative stress are results of disruption to the redox circuitry due to the imbalance between antioxidants and pro-oxidants. These, in turn, leads to damage in macromolecular levels (71). RIS levels elevation are marked in AD, in which redox-active metal ions like iron and copper ions are observed to bind to beta amyloid peptides. Further elevation of RIS via reactions of Fenton-type after this (72). NADPH oxidases, mitochondria and endoplasmic reticulum represent the cellular sources for production of ROS. In AD, dysfunction in the mitochondria and reduction of antioxidant enzymes activity have added to oxidative stress augmentation (73). In recent studies, evidence have suggested that oxidative stress mitigation with the help of natural and synthetic

antioxidants might as well become a new approach to therapy in AD (74). The mechanisms and role of ROS in AD is represented in Figure 1.4.

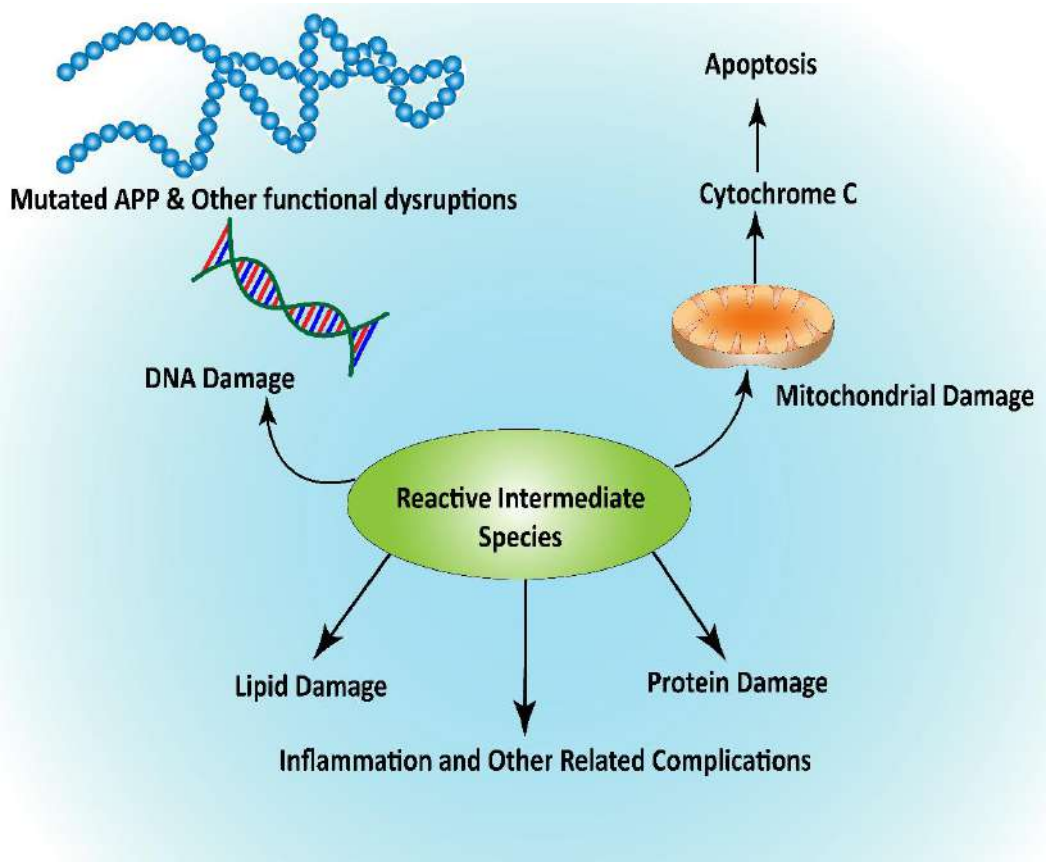

Figure 1.4 Role of Oxidative stress in the pathogenesis of AD

e) Role of calcium and cholesterol

In brain, calcium ions are an essential co-factor in many kinases, proteases and phosphatases reactions. Playing very crucial role in memory with respect to short-term memory and long-term potentiation and learning. And increased levels of this calcium ions within the neuronal cells due to beta amyloid causes neurotoxicity and failure of the synapses (75). In the analysis of the post-mortem of the AD affected brain has shown indications of abnormalities in calcineurin, which is a calcium ion dependent- protein phosphatase which is a critical entity for T-cell signalling and involvement in the beta amyloid induced cognitive dysfunction (76). Demonstrations of overload in mitochondrial matrix via receptor mediated internalization accumulates calcium ions in excess. This results in the multifactorial diseases development like AD, due to severe calcium ion dysfunctional homeostasis (77).

Lipid molecules, such as cholesterol, which forms the cell membrane foundation, is a precursor for steroid hormones, bile acids and vitamin D synthesis (78). Intermediary mevalonate is an exceedingly complex route for cholesterol production. This mevalonate is mediated by HMG-CoA reductase pathway (79). Even though, mevalonate is an essential constituent for normal body physiology, the high levels can be predisposed to the development of AD. There is evidence that indicate treatment with cholesterol has resulted in the increase level of human APP expression, and, in that same time, it reduces, APPs-alpha production. There is an enhancement in alpha-secretase activity during cholesterol removal. Modulation of beta and gamma secretase in the beta amyloid production and increased production and aggregation levels is also done by cholesterol (80). There is an enhancement of the degradation and internalization of beta amyloid by low cholesterol. While elevated levels encourage the extracellular amyloid aggregation. There are some amino acids of beta-amyloid that form pore via binding cholesterol in the membrane. These effects have an underscore involvement of cholesterol in the development of AD (81).

f) ER stress

The endoplasmic reticulum facilitates the folding, quality assurance, synthesis and subcellular trafficking of proteins. Glycosylation within the endoplasmic reticulum, notably, determines the fate of the protein. For synaptic transmission to occur, the ER is the one that controls the ionic equilibrium of the intracellular calcium in the neurons (82). ER, is said to be a significant storehouse for cellular calcium ions. It regulates the concentration of this intracellular Ca^{2+} and maintain the dynamics through all its channels. Neurons that are affected with abnormal homeostasis of calcium ions, not only affects the release of neurotransmitter but also change the signalling pathways that are taking place intracellularly, ultimately. This leads to the neurodegenerative diseases like the AD (83).

The protein quality at various stages of processing is maintained by the endoplasmic reticulum. It is done by functional sorting and proteins that are damaged to all the sites that are appropriate and pathways that follow degradation. The diseases of neurodegenerative nature are often connected with the aggregation and misfolding of the proteins into species that are toxic in nature (84). Some studies done enlightened about the fact that events that are pathological origin, inclusive of the fact of the accumulation of tau, calcium homeostasis disruption and beta-amyloid, all majorly contribute to the stress in the endoplasmic reticulum and cell death subsequently, with special attention to AD (85).

ER stretches, anatomically, from soma to axons and dendrites, where it as a very crucial role to maintain the levels of cytosolic calcium ions in the neuronal cells. The enzyme that maintains the homeostasis of calcium ions in the endoplasmic reticulum for the uptake is Ca-ATPase and for release are RyRs and IP3Rs. In AD mouse models, it

is observed, through research and studies, that there is a dysregulation of calcium ions influx. The analysis of mRNA revealed that AD and MCI cases had high levels of RyR expression (86). It has been demonstrated, via in vivo, that when there was a deletion of RyRs gene in the younger mice models the phenotypes of AD worsens and in the older mice models, there is diminished symptoms. When there are interactions between mGluR5 receptor and beta amyloid, there is an increased level of calcium ions, that further gets connected to calcium ions with pathologies of AD (87). There is a membrane protein sensor, in the endoplasmic reticulum, for example, ATF6, Ire1, and PERK, that, detects the misfolded proteins which later brings the unfolded protein response (UPR). This UPR kinases get over-expressed, in the neurons present in the hippocampus in the patients suffering from AD (88). In in vitro and in vivo studies, further, shows that oligomers of beta-amyloid induce stress in ER- mediated death of the cell.

In the models used for AD, the beta amyloid causes stress in the ER and cholesterol that is perturbed in trafficking via mitochondria are factors that are significant in the progression of the disease. Stress of the ER often influences the processing of APP and its sorting, with further enhancement of the pathology of the AD, as a result. Moreover, upregulated levels of pPERK, within the neurons, also observed, increased levels of GSK-3-beta, which is a kinase that is linked to tau hyperphosphorylation and formations of NFT (89).

Stress in the Endoplasmic reticulum, activates inflammatory responses in the cellular levels, by toll like receptors (TLRs) and oligomerization of nucleotide domain like receptors (NLRs). With respect to the synthesis of the cholesterol, there is an invaluable role of ER in physiological function, in its malfunctioning there is a direct association of AD with it. With this altered functioning of the neurons, often associating with neurodegeneration, occurs during ER degradation under the stress (90). With all the broad-spectrum factors that contributes to the stress in ER and AD pathology, that are targeting ER-stress can be seen as a potential strategy to treat Alzheimer's. With all the recent approaches that are developed to achieve this goal, includes the use of chaperones that are synthetic in nature to help reduce the UPR, ER stress and targeted homeostasis of calcium to help minimize the death of the cells that are originating from ER stress. Even though there is less evidence for ER stress targeting for AD treatment, the most predominant role that ER stress plays in the pathogenesis of AD makes it one of the potential targets for therapy (91)

g) Effects of telomerase and cholinergic toxicity

The end of the chromosome is termed as telomere that houses protective TAG repeats that are lost during every cell division. It contributes to senescence of the cell via oxidative stress and inflammation (92). For telomeres to resist any kind of erosion, a ribonucleoprotein, telomerase, which is made up of TERT, also known as telomerase reverse transcriptase; and TER which is an RNA template, helps in inserting the repeats

(93). The crucial events in AD that are related to shortening of telomere is very well documented. The oligomers of beta amyloid, that are water soluble, inhibits the elongation of the telomere by prevention of the complex, famously known as, DNA-DNA-telomerase. Therefore, blocking the activity of the telomerase in the neuronal cells. And promoting senescence and, therefore, neurodegeneration (94).

Toxicity due to cholinergic, distorts the cholinergic neurons. These neurons are critically crucial within the brain because of their involvement in the diverse processes of intelligence, like attention, learning, memory, response, elaboration of the sensory information and sleep (95). Peter Davies and A.J.F Maloney, in 1976, came across the dysfunction of cholinergic neurons, neurochemically in AD (96). There was a comparison done by them between neurotransmitter-synthesizing enzymes from AD and the normal brains. From this study, they found out, that most of the enzymes apart from ChAT, did not change in AD and the brain that is normal, declined significantly in brain affected with AD by approximately 30-90%. This enzyme ChAT, catalyses, the synthesis of ACh, acetylcholine, which is a neurotransmitter, from acetyl- CoA, ATP and choline. The lowered activity of ChAT led to deficiency of ACh, which caused synapse impairment and transmission of synapse. AChE, acetylcholinesterase, hydrolyses the molecules of ACh at the synaptic cleft (97,98). When there is an imbalance between the ChAT activity during the ACh generation and AChE during its breakdown, causes depletion of ACh in the hippocampus, amygdala and cortex in AD, therefore affecting cognitive functions. Hence, targeting the dysfunction of cholinergic, is a strategy, potential enough to mitigate the decline in the cognitive behaviour in AD patients. The first AChE inhibitor is, tacrine, that was FDA-approved for AD treatment. At present, all the approved AD drugs function as AChE inhibitors (99).

5. Treatment of comorbidities

Comorbid sleep disorders, such as obstructive sleep apnoea, should be treated using oral appliances or nasal devices that create expiratory positive airway pressure; patients with dementia may have difficulty adapting to sleeping with a mask. Comorbid gait and balance disorders in persons with presumed AD should raise questions about alternative diagnoses such as Lewy body disease, normal pressure hydrocephalus or cerebrovascular disease. The treatment of pain in persons with cognitive impairment is challenging owing to the difficulties that persons with dementia have in describing their pain, as many potent analgesic agents may cause sedation or reduced attentional abilities, there are substantial limitations on the use of medications beyond acetaminophen and NSAIDs (100).

A) Pharmacological approaches for AD

Pharmacological approaches that are specific to AD are limited to three cholinesterase inhibitors (donepezil, rivastigmine and galantamine) and the NMDA

receptor antagonist memantine. donepezil is also approved for severe dementia only in the USA. The adverse effects of the cholinesterase inhibitors include nausea, vomiting, loose stools or loss of appetite in a minority of individuals and, less commonly, muscle cramps, headaches and unpleasant dreams. Memantine is approved in the USA only for moderate to severe dementia due to AD; its effects are also rather modest. The adverse effects of memantine are minor (101).

One drug, aducanumab (a monoclonal antibody that targets Aβ protofibrils), is being considered by the FDA and the EMA for AD based on the results of two phase III clinical trials. Donanemab which targets plaque Aβ, reported both a lowering of aggregated Aβ and a reduction in the rate of cognitive and functional decline in a phase II study; a larger phase III trial (NCT#04437511) is under way. Behavioural alterations in persons with dementia due to AD, usually in the moderate to severe stages, is a particular challenge to manage. Frightening hallucinations, delusions that lead to socially disruptive behaviours or physically aggressive behaviours will invariably require pharmacological intervention. Pimavanserin, a selective serotonin inverse agonist, is currently approved in the USA and Europe for Parkinson disease dementia psychosis but it is being examined in the USA for a broader indication to include dementia- related psychosis in general (102).

b) Quality of life

The degree of cognitive impairment in AD has a dramatic effect on the patient's desires and abilities to engage in some activities. MCI and dementia are a family affair and quality of life is as much of an issue for the primary family caregiver as it is for the patient. The stress of a diagnosis of MCI or dementia may be especially high in families in which the patient is under the age of 65 years and who had been working or had dependent children still at home (2). The quality of life of both patient and caregiver is affected by several factors such as other comorbidities, physical limitations, hearing limitations, visual limitations, mood disorders, pain disorders and sleep dis orders. Volunteer organizations such as the Alzheimer's Association and the Alzheimer's Disease International can be a resource for providing consultation to families of persons with dementia. In some cases, traditional therapies such as Chinese medicine, ayurvedic herbs, homeopathies, yoga etc are implemented in order to enhance the quality of life of the patients suffering from AD (103).

Conclusion

AD is a 100-year-old known disease, yet it has still not come to the bottom line about how to treat it. Most of the reasons are complex pathophysiology and multifaceted nature of Alzheimer's disease. Various novel strategies are being discovered by all the recent studies being done. Targets are being reportedly adapted to overcome burdens like secretase enzymes, targeted neuroprotein, sirtuins, targeting the inflammasomes, TRL

mediated inflammations, mitochondrial biology, sphingolipids, and many more are on the list. There are questions that are yet to be answered. Questions like the identification of the predominant state of beta-amyloid in the intra-neuronal regions; how and when it is affecting the learning, memory, all the somatic abilities, synaptic transport and the difference seen in young people. In future, perspectives where studies can be done shall have an aim to identify the targets, excretion patterns, their secretions and the utilization of these substances as protectant to reduce neuronal declination.

Acknowledgement

The authors would like to express their sincere gratitude to *Deep Science Publisher* and the editorial team of this book for their invaluable support in the final publication process and for providing the opportunity to contribute to this esteemed volume.

Conflicts of Interest

The authors declare that there are no conflicts of interest related to this work.

Funding Source

No funding was received for the preparation of this book chapter.

Author Contribution

All authors have contributed equally to the conception, preparation, and completion of this book chapter.

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