The Progression of Alzheimer's Disease: A Comprehensive Review

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Abstract

AThe most common form of dementia worldwide is AD (Alzheimer's disease). Currently, over 55 million people worldwide are living with dementia, and this is projected to more than triple by 2050. It is a slowly progressive neurodegenerative disease, defined by the build-up of amyloid-beta (A) plaques, neurofibrillary tau tangles, inflammation, loss of synapses, and neurons. The disease occurs along a continuum, starting from the preclinical stages of the disease, leading to mild cognitive impairment and eventually the full disease of dementia, with pathological changes occurring decades before the onset of clinical symptoms. We look at genetic risks for AD (e.g., APOE4) as well as cardiovascular and modifiable lifestyle risks. We look at the current treatment strategies that are FDA approved: cholinesterase inhibitors, memantine, and the newly approved anti-amyloid monoclonal antibodies, lecanemab and donanemab, as well as emerging new treatments, non-pharmacological treatments, and preventions. To identify new therapeutic targets to prevent, delay, or modify the disease course and to formulate management strategies, we must appreciate the complex, multifactorial nature of AD.

Keywords: Alzheimer's disease, amyloid-beta, tau protein, neurodegeneration, risk factors, biomarkers, treatment, prevention.

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease and the leading cause of dementia in individuals 65 years of age and older. It was first reported by Alois Alzheimer in 1906, and it has grown from an obscure clinical phenomenon to a massive societal health crisis impacting the health systems, economies, and cultures of nations throughout the world. Alzheimer's is defined by its progressive cognitive and behavioural impairment and functional deterioration leading to a terminal state. [1]. The traditional pathological features that define Alzheimer's disease are extracellular amyloid-beta (A) protein deposits in senile plaques and intracellular hyperphosphorylated tau protein aggregates in neurofibrillary tangles (NFTs). It is widely understood now that Alzheimer's is an even more complex disease with multiple interconnected pathomolecular mechanisms, including but not limited to, mitochondrial dysfunction, oxidative stress, neuroinflammation, synaptic loss, blood-brain barrier dysfunction, and dysregulated metabolism [2]. The economic and social cost of Alzheimer's disease is truly catastrophic. Current global estimates suggest that 55 million people have dementia globally, and AD is the cause for 60-80% of these cases. It is predicted that these numbers will reach 152 million by 2050 as the global population ages, and the global costs will continue to increase from over $1 trillion annually in 2018. The emotional and psychological impact on patients, caregivers and families are immeasurable [3].Other than decades of intense investigation and many clinical trials, treatments remain scarce. Until recently, only drugs targeting symptoms with no influence on disease course were available. The 2023 approval of lecanemab and the 2024 approval of donanemab by the FDA, were considered the first disease-modifying drugs and provided a small slowing in cognitive decline [4]

2. Pathophysiology of Alzheimer's Disease

2.1 The Amyloid Cascade Hypothesis

The amyloid cascade hypothesis has been the principal theory driving Alzheimer's disease research for more than 30 years, suggesting that the accumulation of Ab peptides is the initial event that triggers AD pathology. Ab is generated from the sequential processing of amyloid precursor protein (APP) by, or -secretase (BACE1) and γ-secretase enzymes. This processing generates various forms of Ab peptide, of which the A40 and A42 forms are the most abundant, with A42 being the form more susceptible to aggregation and neurotoxicity. Under normal physiological circumstances, Ab production and clearance exist in a homeostatic balance, which is dysregulated in AD, leading to the accumulation, oligomerization, and formation of insoluble Ab plaques. It is thought that the soluble Ab oligomers are the neurotoxic species responsible for disruption of synaptic function, induction of oxidative stress and elicitation of inflammatory responses before plaque formation.Recent works have revised the amyloid hypothesis to account for the idea that Ab pathology alone does not fully encompass all aspects of AD. This is reflected by the 2024 revised Alzheimer's Association criteria: this uses a biological stage framework that includes both amyloid and tau biomarkers, taking into account heterogeneity, co-pathologies, and cognitive resilience. [5],[6]

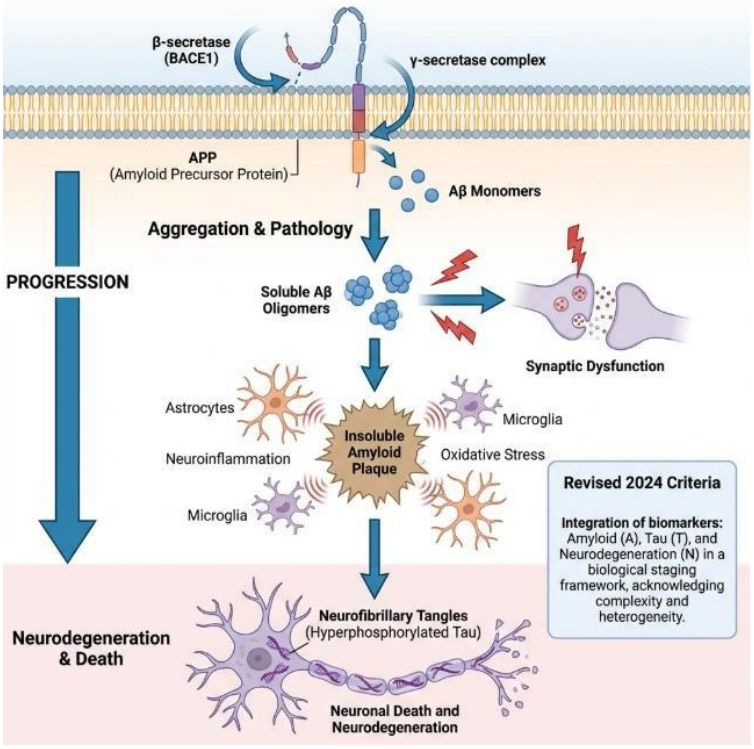

Fig.1 Amyloid Cascade

2.2 Tau Pathology and Neurofibrillary Tangles

Tau Protein and Neurofibrillary Tangles: Tau is a microtubule-associated protein that functions to support neuronal cytoskeletal organization, intracellular signalling, and axonal transport. In AD, tau becomes abnormally hyperphosphorylated, detaches from microtubules, and forms aggregated paired helical filaments that are the hallmark component of neurofibrillary tangles (NFTs). Unlike the relatively static nature of A pathology, tau pathology expands over time to anatomically connected areas of the brain in a progressive and predictable way (Braak staging). The spatial pattern of tau deposition and propagation through the brain is highly correlated with cognitive decline and neuronal loss, more so than A burden. Although A likely initiates the cascade of disease, tau pathology likely drives subsequent neurodegeneration, leading to clinical progression. Indeed, recent work has suggested that A oligomers may act to increase the phosphorylation and propagation of tau in an iterative loop. P-tau has been recognized as a central marker for the presence of AD, with specific phosphorylated tau species, p-tau217, p-tau181, and p-tau231 showing significant potential for diagnosis and tracking. Importantly, these p-tau biomarkers are now reliably detectable in both CSF and blood.[7],[8],[9]

2.3 Neuroinflammation and Microglial Dysfunction

Neuroinflammation is an essential part of the pathogenesis of AD, and its main cellular effectors are microglia. The resident immune cells of the brain, microglia, usually exhibit a protective function, such as the clearance of cellular debris through phagocytosis, pruning of synapses, and neuroprotection. However, chronically activated microglia have a detrimental impact on the brain in AD, sustaining a prolonged inflammatory reaction that underlies neurodegeneration. Activated microglia have been found to aggregate at the sites of A plaques and to secrete pro-inflammatory cytokines (such as IL-1, IL-6, and TNF-) and the formation of reactive oxygen species (ROS), contributing to neurotoxicity. This chronic inflammatory response creates a self-sustaining loop that promotes accumulation of A, phosphorylation of tau, and neuronal injury. Multiple AD risk genes have been discovered that are involved in microglial functions and innate immune responses, including TREM2, CD33, and CR1. There is emerging evidence to support the view that microglia are not homogeneous but possess a range of activation phenotypes rather than just the standard M1/M2 polarization. Microglia adopt a specific state known as disease-associated microglia (DAM) during neurodegeneration, which has been associated with a specific gene expression profile and functionally distinctive properties. The study of the diversity of microglial states and their dynamic changes holds promise as therapeutic strategies for control of neuroinflammation.[10],[11]

2.4 Mitochondrial Dysfunction and Energy Metabolism

Mitochondrial dysfunction and impaired energy metabolism are early and striking features of AD. Neurons have a high energy demand due to the tremendous energetic requirements of the brain and therefore are very susceptible to mitochondrial dysfunction. Multiple aspects of mitochondrial function are disrupted in AD, including oxidative phosphorylation, ATP production, calcium homeostasis, and mitochondrial dynamics (fission, fusion, and mitophagy).Decreased brain glucose metabolism is detectable via FDG-PET, several years prior to clinical manifestation of AD. Glucose hypometabolism in AD is most pronounced in temporoparietal areas and it leads to synaptic dysfunction and neuronal susceptibility to death. Mitochondrial dysfunction results in increased ROS

production, which leads to oxidative damage of lipids, proteins, and DNA, and exacerbates disease pathogenesis.It has also become evident that there is a reciprocal relationship between mitochondrial dysfunction and AD pathology. An oligomer and hyperphosphorylated tau can induce mitochondrial dysfunction and dysfunction of mitochondria can further lead to enhanced A production and tau hyperphosphorylation. This vicious cycle will therefore exacerbate the development of AD. Mitochondrial enhancement offers potential therapeutic targets.[12],[13],[14]

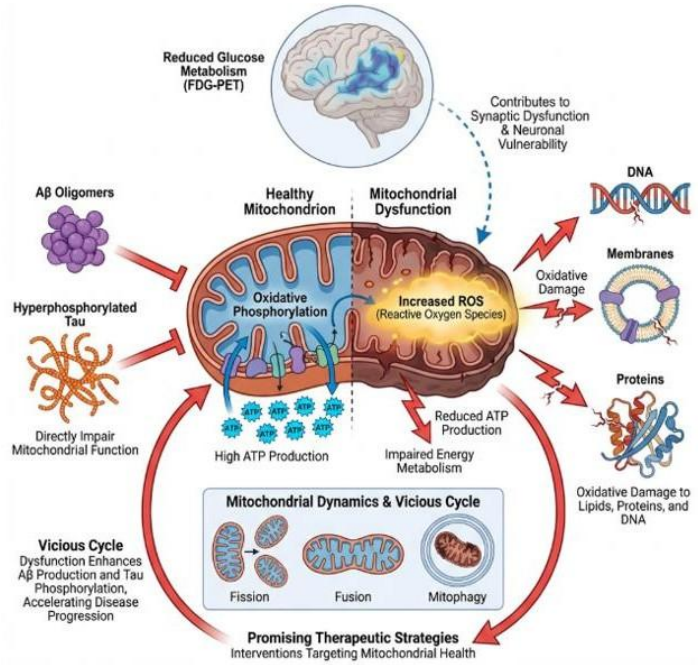

Fig.2 Mitochondrial Dysfunction and Energy Metabolism in Alzheimer's Disease

2.5 Synaptic Dysfunction and Neuronal Loss

Synaptic loss appears to be the best neuropathological correlate of cognitive deficit in AD, with it predating neuronal death. Dendritic spines (the postsynaptic sites of excitatory synapses) are also highly susceptible to damage in AD. They are known to exhibit specific patterns of association with tau pathology (that is, they are clustered around it), thus implying tau-mediated synaptic injury.[15]. Aß oligomers (soluble ones at least) are shown to have a strong affinity to synapses, where they are responsible for LTP dysfunction, an alteration of neurotransmitter release, and receptor trafficking. They have a destabilizing effect on synaptic plasticity (the cellular basis of learning and memory), and the expression and localization of multiple proteins in the postsynaptic density (PSD-95, neurogranin), presynaptic region (synaptophysin, SNAP-25), and adhesion molecules are altered in AD. [16]. The reasons why certain neuronal populations and regions of the brain are susceptible to damage over others are complex and likely related to metabolic demand, neuronal connectivity and the differential expression of risk genes, among other things. Neurons in the hippocampus and entorhinal cortex are among the earliest to be damaged and this correlates to the typical early presentation of AD as an episode memory impairment. Elucidating mechanisms of neuronal vulnerability/resilience provides a potential therapeutic avenue for neuroprotection.[17]

2.6 Vascular Contributions and Blood-Brain Barrier Dysfunction

Vascular pathology frequently co-exists with AD neuropathology and makes a considerable contribution to cognitive dysfunction. Cerebrovascular dysfunction is characterized by decreases in cerebral blood flow and impairment in neurovascular coupling, breakdowns in the blood brain barrier (BBB) and cerebral amyloid angiopathy. These cerebrovascular changes can develop early in AD and synergize with AD pathology.[19] BBB breakdown allows peripheral immune cells and inflammatory factors to enter the brain and promote neuroinflammation. In addition, disruption of A clearance across the BBB will promote an accumulation. The relationship between vascular risk factors (hypertension, diabetes and atherosclerosis) and AD is well established, and they may advance the disease process by inducing changes such as hypoxia, inflammation, and metabolic perturbations. The glymphatic system is a newly identified pathway for waste clearance within the brain, which provides another avenue through which brain vascular function, sleep, and AD can be linked. Glymphatic clearance operates most effectively during sleep and is responsible for removing A as well as other metabolic wastes. It can be disturbed by aging, cerebrovascular disease and sleep disruption, which may consequently play a role in the accumulation and the development of AD. [18]

3. Disease Progression and Clinical Stages

3.1 The Alzheimer's Continuum

At present, AD is believed to be a continuous process that occurs on a continuum starting at preclinical AD and ending in dementia, also with MCI in between. This has been updated to include in the 2024 Alzheimer's association criteria and that there is pathology in the brain for 15-20 years before any clinical presentation. The

progression is then classified as:
Preclinical AD-The individual has the pathology for AD (buildup of A, tau, or both) but no cognitive impairment. However, some with preclinical AD may complain of subjectively impaired cognition (SCD) without evidence of objective impairment on cognitive testing. Based on biomarker data, roughly 20-40% of older adults who are cognitively normal already have preclinical AD.
Prodromal AD (MCI due to AD): Subject has objective cognitive decline (most commonly an episodic memory deficit) but is independent in daily activities. An estimated 10-15% of individuals with MCI develop AD dementia per year, although this is quite variable and dependent on biomarkers.
AD dementia: Decline is severe enough to cause significant impairment in function and the loss of independence in daily activities. AD dementia exists as mild, moderate, and severe forms; average lifespan after diagnosis is 4-8 years, but with a significant range. (20)

Table:1 Cognitive vs Functional Decline Stages in Alzheimer's Disease

Disease Stage	Cognitive Decline	Functional Decline
Preclinical AD	No obvious clinical symptoms Subtle memory inefficiency may be detectable on sensitive tests Biomarker positivity (Aβ, tau)	Normal daily functioning Independent in all ADLs and IADLs
Mild Cognitive Impairment (MCI) due to AD	Episodic memory impairment (recent events, conversations) Mild deficits in attention and executive function	Mild difficulty in complex IADLs. Problems with finances, medication management, and planning.
Mild Alzheimer's Dementia	Marked memory loss Language difficulties (word-finding, naming) Impaired visuospatial skills Reduced insight	Impairment in most IADLs. Difficulty with shopping, cooking, and transportation Requires occasional assistance
Moderate Alzheimer's Dementia	Severe memory impairment. Disorientation to time and place. Executive dysfunction.	Dependence in basic ADLs. Assistance required for dressing, bathing, toileting.
Severe Alzheimer's Dementia	Profound cognitive impairment. Minimal verbal communication. Loss of recognition of family members. Severe BPSD	Complete dependence. Loss of ambulation and swallowing. Bedridden Complications: infections, aspiration pneumonia

3.2 Biomarker Staging and Disease Trajectory

ATN biomarkers can define stages based on the status of amyloid (A), tau (T), and neurodegeneration (N) for an individual and gives a biological stage that does not correlate directly with the clinical stage.21 This is useful to identify individuals in the preclinical state and for prediction of progression.22 Studies involving staged cohorts have shown that the biomarkers develop in a relatively consistent order (the A, T, N, and finally cognitive changes).[23] Although this general pattern exists, an individual's course is likely to be very heterogeneous. [24] Some individuals possess high pathology with little or no clinical signs of dementia, displaying cognitive reserve. Others with little pathology can show remarkably fast disease progression. [25] This heterogeneity is likely due to factors such as genes, cognitive reserve, pathologies (vascular, LBD, TDP-43), etc. (26)(27)(28)

3.3 Cognitive and Functional Decline

Early AD will typically show a profile of episodic memory loss, the earliest involvement of regions being the hippocampus and entorhinal cortex. (29) The range of impairment widens in later disease and also affects language, visuospatial abilities, executive function and attention.
(30) The presence of BPSD is common in the majority of sufferers and include depression, anxiety, apathy, aggression, agitation, psychosis and sleep disturbances. (31) The decline in functional abilities follows the typical pattern: in the early stages, impairment is seen in IADLs such as financial affairs, medication management and use of transport, (32), (33). As the disease progresses, impairment occurs in the ADLs; eating, dressing, bathing and toileting need assistance, (34). The advanced stage patient becomes completely dependent, eventually losing the ability to ambulate or swallow which can lead to infection, aspiration and pneumonia (35)

4. Risk Factors for Alzheimer's disease

4.1 Genetic Risk Factors

APOE genotype: Genetic risk factor that shows the greatest effect on late-onset AD. Carriers of the APOE 4 allele are 3-4 times more likely to develop AD compared to non-carriers in heterozygous state, 8-12 times more likely when homozygous. Protective effect seen in the 2 allele. 65% of patients with AD carry at least one copy of APOE 4[36-38]. The APOE4 genotype is implicated in many disease mechanisms including clearance of A, tau pathology, neuroinflammation, lipid metabolism,BBB function, mitochondrial function [39-41]. Recent research has revealed that APOE4 carriers develop pathology earlier and have a faster disease progression and characteristic regional distribution of brain atrophy compared to non-carriers [42,43], the difference in the former appears to be sex-specific and that women are more susceptible to APOE4 associated neurodegeneration [44]. APOE genotype has an impact on therapeutic intervention; APOE4 carriers exhibit increased rates of ARIA with anti-amyloid monoclonal therapy [45, 46]. The identification of APOE mechanisms in disease has identified new targets for therapy and the criteria to treat in AD [47].

Rare genetic variants: Family members of families affected by autosomal dominant forms of EOAD, where a person inherits a mutation in one of APP, PSEN1, or PSEN2 that results in the development of AD before age 65 typically in<1% of cases[48,49]. These mutations result in deterministic AD. Study of EOAD families has been invaluable in understanding AD pathology and the trajectory of biomarkers in AD [50].

Polygenic risk: As well as the effect of APOE on risk of developing AD, GWAS studies have identified >75 genes whose associated variations correlate to the risk of developing AD[51,52]. Many of these are genes implicated in biological mechanisms such as immunity (TREM2,CD33, CR1) lipid metabolism (CLU, ABCA7) endocytosis (PICALM, BIN1) and tau biology (MAPT)[53-55]. The use of polygenic risk scores combining many small effects on risk will increase predictive ability beyond that provided by APOE alone [56].

4.2 Cardiovascular and Metabolic Risk Factors

Hypertension: Midlife hypertension is a major modifiable risk factor for AD and increases risk for AD by 40-60% in several studies. [57-59] The mechanisms by which hypertension affects AD pathogenesis include BBB damage, impaired cerebral blood flow, vascular damage and the development of vascular pathology and AD neuropathology. [60,61] With progression of the disease blood pressure changes. It has been demonstrated that late-life hypotension is associated with more rapid decline and this is suspected to represent effects on the autonomic nervous system by the disease. [62,63]

Diabetes Mellitus: Type 2 diabetes increases AD risk by approximately 1.5-2-fold. [64,65]. The proposed mechanisms involve insulin resistance and changes in A and tau metabolism, inflammation, oxidative stress and vascular complications. [66- 68] This has led to the suggestion that AD is "type 3 diabetes" because of insulin resistance occurring in the brain. Management of diabetes and the administration of insulin-sensitizing medications are possible prevention strategies. [69,70]

Obesity and Metabolic Syndrome: Midlife obesity increases AD risk, and although associations are somewhat conflicting with late-life obesity appearing protective possibly due to effects of weight loss due to the disease [71-73]. Combined with obesity, metabolic syndrome, which is characterized by a constellation of dyslipidemia, hypertension, and insulin resistance, carries a greater risk of dementia as each feature contributes cumulatively to the development of dementia and involves inflammatory and oxidative mechanisms. [74,75]

Dyslipidemia: The associations between cholesterol and AD are still complex and controversial. Midlife hypercholesterolemia is thought to increase the risk of AD, whereas associations with late-life may be less convincing. [76,77] Results for the use of statins for prevention are mixed among observational and intervention studies. [78,79] The biochemical associations between
cholesterol metabolism and the processing of APP and A metabolism add to the mechanistic plausibility. [80,81]

Conclusion:

Alzheimer's disease (AD) represents one of the most daunting problems in medicine, affecting millions across the globe in devastating personal and societal ways. The last decade has produced a revolution in our knowledge of the pathophysiology of AD with understanding the complex interrelationships between genetic risk factors, aging processes, metabolic dysfunction, vascular pathology, inflammation and lifestyle influences. Combined, these factors define a person's risk of developing AD and dictate the rate at which the disease will progress.

Much has been accomplished. We are closer than ever before to achieving easily accessible and scalable detection of AD with the development of blood-based biomarkers. With the recent FDA approvals of lecanemab and donanemab we now have proof-of-principle that the disease course can be altered by removing the amyloid plaque with the inherent but modest therapeutic effect of the drug suggesting much more therapeutic improvement is needed and achievable. In addition, the realization of many preventable risk factors for AD suggests that risk reduction will soon become a realistic goal through lifestyle modification and management of cardiovascular risk factors.

Significant challenges, however, still exist. Existing disease-modifying therapies are minimally effective and face several issues including ARIA and its associated risks, high cost and requirement for administration in early disease. There have been many recent disappointments with drug development programs, specifically in tau-targeting therapies and the gulf between promising pre-clinical work and successful clinical translation remains substantial. Health equity remains a major problem with minority populations being underrepresented in clinical research and facing barriers to diagnosis and treatment.

Successful advancement of the field in the coming years will likely be the result of multi-pronged approaches.

Combination therapy targeting multiple pathological processes at once will be a necessary strategy. Targeting of AD at even earlier, pre-clinical stages, will require innovative and ethical methods for trial design, as may more personalized approaches that utilize an individual's specific risk factors, disease sub-type and biomarker profile. Lifestyle modification will be key to the population-wide prevention of AD.

Substantial research investment, inventive clinical trial designs, technological advancements, equitable treatment strategies and inter-sectorial collaboration between academic, industrial, government entities and patient advocacy groups are required. While still a devastating illness, there is now hope for a successful approach to the prevention, slowing or even stopping of the development and progression of AD.

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