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Alzheimer Disease: An Integrated Multidisciplinary Perspective on Pathophysiology, Diagnosis, Management, and Contemporary Therapeutic Advances for Pharmacists, Neurologists, Nurses, Health Information Professionals, and Healthcare Assistants

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Abstract

Background: Alzheimer disease is a progressive neurodegenerative disorder characterized by cognitive decline, neuronal loss, amyloid-beta accumulation, neurofibrillary tau pathology, and progressive functional deterioration. Its increasing prevalence among older adults represents a growing global health burden. Advances in understanding the molecular, cellular, genetic, and pathological mechanisms of Alzheimer disease have improved approaches to diagnosis, biomarker development, and therapeutic intervention.

Aim: This article aims to provide an integrated academic overview of Alzheimer disease, focusing on its epidemiology, etiology, pathophysiology, histopathological characteristics, clinical assessment, diagnostic evaluation, and current management approaches.

Methods: A narrative review approach was used to synthesize information concerning the biological mechanisms, clinical manifestations, diagnostic methods, pathological characteristics, and therapeutic strategies associated with Alzheimer disease. The review incorporated clinical, biochemical, genetic, neuroimaging, and neuropathological perspectives to provide a comprehensive description of disease development and management.

Results: Alzheimer disease involves interacting mechanisms that include amyloid-beta accumulation, abnormal tau phosphorylation and aggregation, cholinergic dysfunction, synaptic degeneration, neuronal loss, neuroinflammation, vascular pathology, and genetic susceptibility. Increasing age represents the principal epidemiological risk factor, while APOE ε4, cardiovascular disease, diabetes, obesity, and family history contribute to disease susceptibility. Diagnosis integrates clinical assessment, cognitive testing, laboratory investigations, structural and functional neuroimaging, and selected amyloid and tau biomarkers. Current management includes cholinesterase inhibitors, memantine, behavioral interventions, lifestyle measures, and emerging amyloid-targeting disease-modifying therapies.

Conclusion: Alzheimer disease represents a multifactorial neurodegenerative disorder requiring integrated diagnostic and therapeutic strategies. Earlier identification of pathological changes and continued development of disease-modifying interventions may improve clinical outcomes and reduce disease burden.

Keywords: Alzheimer disease, dementia, amyloid-beta, tau protein, neurodegeneration, cholinergic dysfunction, biomarkers, neuroimaging, cognitive impairment, disease-modifying therapy.

Introduction

Dementia represents a broad clinical syndrome characterized by a persistent and clinically significant decline in one or more cognitive domains that ultimately interferes with an individual's ability to function independently in everyday life. The syndrome may affect memory, language, executive functioning, attention, perception, reasoning, judgment, and social or behavioral functioning. Dementia is not a single disease but rather a clinical manifestation that can result from several neurodegenerative, vascular, metabolic, infectious, traumatic, and other pathological processes. Among the various causes of dementia, Alzheimer disease

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(AD) remains the most prevalent and extensively investigated neurodegenerative disorder. AD accounts for at least two-thirds of dementia cases among individuals aged 65 years and older and represents one of the most important causes of progressive cognitive impairment in aging populations. The condition is characterized by an insidious onset and gradual progression, with pathological and neurobiological changes often developing for years before the emergence of clinically apparent symptoms. Alzheimer disease is fundamentally associated with progressive deterioration in cognitive and behavioral functioning. The disease commonly affects episodic memory during its earliest clinically recognized stages, although its manifestations extend beyond memory impairment as neurodegeneration progresses. Individuals may experience deterioration in comprehension, language, attention, reasoning, judgment, executive functioning, visuospatial processing, and behavioral regulation. These impairments progressively compromise the individual's capacity to perform occupational, social, and personal responsibilities. Although AD may not directly produce death in the same manner as an acute catastrophic illness, progressive cognitive and functional deterioration substantially increases susceptibility to secondary complications. Advanced disease may result in immobility, malnutrition, aspiration, infection, injuries, and other medical complications that ultimately contribute to mortality. Consequently, the clinical burden of AD extends beyond cognitive impairment and encompasses progressive loss of independence, increasing caregiver dependence, healthcare utilization, and vulnerability to life-threatening complications [1][2][3].

The public health importance of Alzheimer disease has increased substantially with population aging and improvements in survival from many other chronic diseases. According to data from the Centers for Disease Control and Prevention, Alzheimer disease was ranked as the seventh leading cause of death in the United States in 2022, whereas COVID-19 ranked fourth during that period. Before the COVID-19 pandemic, AD was identified as the sixth leading cause of death, following stroke [1]. These mortality statistics emphasize the growing importance of neurodegenerative disorders as major contributors to population-level morbidity and mortality. However, the impact of AD cannot be evaluated solely according to mortality rankings. The disease often progresses over many years and produces prolonged disability, extensive dependence on family caregivers and healthcare systems, and substantial economic and social consequences. Therefore, its significance is closely associated with both the duration of disability and the progressive loss of cognitive and functional independence. The age at onset of Alzheimer disease provides an important clinical distinction. Most individuals develop symptoms after the age of 65 years, a presentation generally classified as late-onset Alzheimer disease. Late-onset AD represents the predominant form of the disease and is strongly associated with advancing age, although its development reflects interactions among genetic susceptibility, biological aging, vascular factors, environmental exposures, and other mechanisms. Early-onset Alzheimer disease occurs before the age of 65 years and accounts for approximately 5% of individuals diagnosed with AD. Despite its lower frequency, EOAD has substantial clinical importance because it often affects individuals during periods of active employment, family responsibility, and social engagement. Furthermore, early-onset disease may present with atypical clinical manifestations and may not initially follow the characteristic pattern of progressive episodic memory impairment. These atypical presentations can delay recognition and diagnosis, thereby postponing appropriate clinical assessment and management. EOAD is also frequently associated with a more aggressive disease trajectory and more rapid progression in some affected individuals [2].

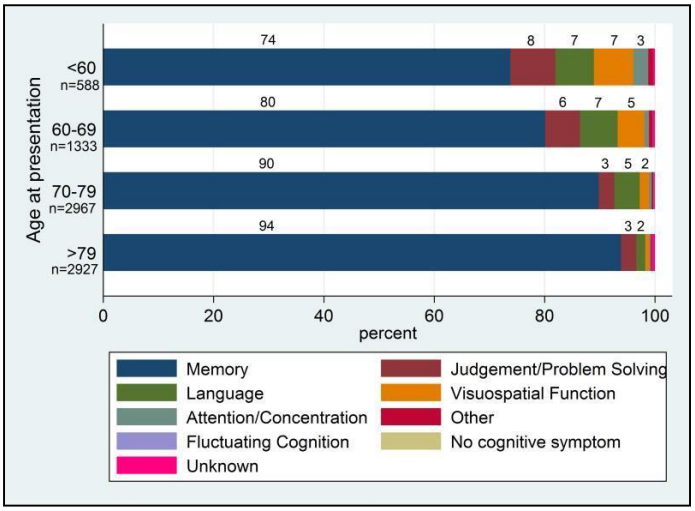

Figure 1: Cognitive symptom Presentation.

The increasing recognition of Alzheimer's disease as a complex biological process has contributed to major developments in diagnostic science. During the past decade, considerable progress has been achieved in the identification and application of biomarkers capable of detecting pathological processes associated with AD before severe clinical impairment becomes evident. Biomarker development has transformed the conceptualization of Alzheimer disease from a condition defined primarily by clinical symptoms into a biological continuum that may be investigated through measurable pathological indicators. Important diagnostic biomarkers include neuroimaging findings obtained through amyloid and tau positron emission tomography, as well as biochemical measurements derived from cerebrospinal fluid and blood plasma. These markers include amyloid-related measures, tau concentrations, and phosphorylated tau levels [3]. The increasing availability of plasma-based biomarkers is particularly

important because blood testing may provide less invasive opportunities for identifying and monitoring pathological changes associated with AD. The clinical value of biomarkers extends beyond diagnostic confirmation. Earlier identification of pathological changes may facilitate differentiation between Alzheimer disease and other causes of cognitive decline, improve prognostic assessment, support participant selection for clinical trials, and enable earlier implementation of therapeutic interventions. Biomarkers have also contributed to the development of treatments designed to influence underlying disease processes rather than exclusively managing clinical symptoms. Despite substantial scientific progress, no definitive cure currently exists for Alzheimer disease. Available therapeutic approaches may alleviate selected cognitive, behavioral, or neuropsychiatric manifestations and improve clinical management. However, recent advances in biomarker science have supported the development of therapies intended to modify the progression of disease, particularly by targeting pathological mechanisms associated with amyloid and other molecular processes [3]. These developments have increased the importance of early and accurate diagnosis because disease-modifying interventions may offer greater benefit when implemented before extensive and irreversible neurodegeneration has occurred.

The clinical progression of AD is commonly conceptualized as a continuum consisting of several stages that reflect increasing pathological burden and functional impairment. The earliest stage is the preclinical or presymptomatic phase, during which biological changes associated with Alzheimer pathology may be present despite the absence of clinically apparent cognitive impairment. This stage is followed in some individuals by mild cognitive impairment, during which measurable decline in cognitive performance is present but functional independence remains relatively preserved. Progression beyond this stage may lead to dementia, characterized by cognitive impairment severe enough to interfere substantially with independent daily functioning. The dementia phase can be further classified as mild, moderate, or severe according to the degree of cognitive deterioration and functional dependence [4]. This clinical staging framework provides a useful representation of disease progression but should be distinguished from formal diagnostic classifications, including criteria described in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [5]. The earliest and most characteristic clinical manifestation of typical Alzheimer disease is impairment of episodic short-term memory. Individuals commonly experience increasing difficulty acquiring, retaining, and recalling recently learned information while relatively remote or long-established memories may remain preserved during the initial stages. A person may repeatedly ask the same questions, forget recent conversations, misplace frequently used objects, or experience difficulty remembering appointments and recently acquired information. These manifestations reflect the progressive involvement of neural structures essential for memory formation and consolidation. As the disease advances, cognitive impairment extends beyond isolated memory dysfunction and increasingly affects problem-solving, judgment, executive functioning, and organizational capacity. The individual may experience increasing difficulty initiating, planning, sequencing, monitoring, and completing complex activities. Tasks requiring sustained attention, multitasking, abstract reasoning, or flexible decision-making may become progressively difficult.

Executive dysfunction has particular implications for functional independence because many activities of daily life depend on intact planning and organizational abilities. Instrumental activities of daily living, including driving, financial management, meal preparation, medication management, shopping, communication, and detailed activity planning, may become impaired relatively early in the disease process. The severity of executive impairment during early AD may vary considerably, ranging from subtle reductions in efficiency to clinically significant dysfunction that compromises safety and independence. These changes may initially be attributed to normal aging, stress, depression, or other conditions, which can contribute to delays in clinical recognition. Progressive impairment eventually becomes increasingly apparent as individuals lose the capacity to manage complex responsibilities that were previously performed independently. Language impairment and visuospatial dysfunction frequently emerge as cognitive deterioration progresses. Language abnormalities may involve difficulty finding appropriate words, reduced verbal fluency, impaired comprehension, or progressive limitations in communication. Visuospatial impairment may affect the ability to judge distance, recognize spatial relationships, navigate familiar environments, or interpret complex visual information. Such deficits can increase the risk of becoming lost, experiencing accidents, or encountering difficulty performing routine tasks. The combined progression of memory, executive, language, and visuospatial impairment ultimately produces extensive functional disability and contributes to increasing dependence on family members, caregivers, and healthcare professionals.

Behavioral and neuropsychiatric manifestations are also important components of the clinical course of Alzheimer disease. Apathy, social withdrawal, agitation, disinhibition, wandering, psychotic symptoms, and other behavioral disturbances frequently become more apparent during

moderate and advanced stages. These manifestations may arise from progressive neurodegeneration affecting neural circuits involved in emotional regulation, motivation, behavioral inhibition, and perception. Neuropsychiatric symptoms can substantially increase caregiver burden and may accelerate the need for continuous supervision or institutional care. Their management often requires comprehensive assessment because behavioral changes may also be influenced by pain, infection, medication effects, sleep disturbance, environmental stress, or other medical conditions. In the later stages of AD, widespread neurological involvement produces increasing impairment of motor and autonomic functioning. Individuals may develop difficulty performing previously learned motor activities, a condition described as dyspraxia. Olfactory dysfunction, sleep disturbances, and extrapyramidal manifestations such as dystonia, akathisia, and Parkinsonian features may also emerge. With continued progression, primitive reflexes may reappear, urinary or fecal incontinence may develop, and the individual may become completely dependent on caregivers for nutrition, mobility, hygiene, communication, and other fundamental activities [6][7][8]. Severe Alzheimer disease therefore represents the final stage of a progressive neurodegenerative process in which cognitive, behavioral, motor, and functional impairments converge to produce profound dependence. Understanding the clinical and biological progression of Alzheimer disease is essential for improving prevention, diagnosis, therapeutic intervention, and long-term care. The development of biomarkers capable of identifying pathological processes during preclinical and early symptomatic stages has created opportunities for earlier recognition of individuals at increased risk of progression. At the same time, the complexity of AD requires continued investigation into its molecular mechanisms, including amyloid accumulation, tau pathology, neuroinflammation, synaptic dysfunction, metabolic abnormalities, vascular influences, and progressive neuronal loss. An integrated understanding of these processes is increasingly important because effective clinical management depends not only on identifying cognitive symptoms but also on recognizing the biological mechanisms that contribute to disease initiation and progression. Continued advances in biomarker discovery and disease-modifying therapy may therefore reshape the future approach to Alzheimer disease by shifting clinical practice toward earlier detection, biologically informed diagnosis, and interventions directed at the underlying mechanisms of neurodegeneration [6][7][8].

Etiology

Alzheimer disease is a progressive neurodegenerative disorder characterized by the gradual loss of neuronal structure and function, ultimately resulting in extensive neuronal death and progressive impairment of cognitive abilities. The pathological process develops over a prolonged period and may begin years before the appearance of clinically detectable cognitive symptoms. Neurodegeneration typically involves brain regions that play central roles in memory formation, spatial orientation, and cognitive integration. Among the earliest affected regions is the entorhinal cortex, which maintains extensive anatomical and functional connections with the hippocampal formation. Progressive involvement of these structures contributes to the characteristic impairment of episodic memory that commonly represents the earliest clinical manifestation of typical Alzheimer disease. As neuronal loss extends to additional cortical and subcortical regions, cognitive dysfunction becomes increasingly widespread and affects executive functioning, language, visuospatial processing, judgment, and behavioral regulation. The etiology of Alzheimer disease is complex and multifactorial, involving interactions among genetic susceptibility, biological aging, metabolic dysfunction, vascular pathology, environmental exposures, and lifestyle-related factors. Although specific molecular mechanisms continue to be investigated, current understanding indicates that AD does not result from a single causative factor in most affected individuals. Instead, disease development reflects the cumulative interaction of multiple biological processes that influence neuronal vulnerability and neurodegeneration. Genetic factors contribute to both early-onset and late-onset forms of the disease. Certain inherited genetic abnormalities may substantially increase susceptibility to early disease development, whereas other genetic variants modify the probability of developing AD later in life. Trisomy 21 is particularly relevant because individuals with an additional copy of chromosome 21 have an increased risk of developing early-onset dementia. This association reflects the contribution of genetic mechanisms to amyloid-related pathological processes and demonstrates the importance of chromosomal abnormalities in modifying the biological risk of neurodegeneration [8][9].

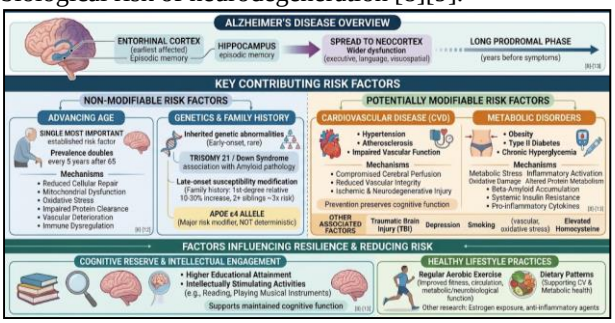

Figure-2: Etiology of Alzheimer's Disease.

Advancing age remains the most important established risk factor for Alzheimer disease. The prevalence of the disorder increases substantially with increasing age, with estimates indicating that the

prevalence of AD approximately doubles for every five-year increase in age after the age of 65 years. Aging itself does not inevitably result in Alzheimer disease, but age-related biological changes can increase susceptibility to pathological processes associated with neuronal dysfunction and degeneration. These changes may include reduced cellular repair capacity, mitochondrial dysfunction, oxidative stress, impaired protein clearance, vascular deterioration, and alterations in immune regulation. The strong relationship between age and disease prevalence explains why population aging is expected to increase the overall burden of AD in many societies. Cardiovascular disease represents another major contributor to the risk of Alzheimer disease and other forms of dementia. Cardiovascular and cerebrovascular disorders can impair cerebral perfusion, compromise vascular integrity, and increase susceptibility to ischemic and neurodegenerative injury. These conditions may also increase the risk of stroke-related cognitive impairment and vascular dementia. Increasing evidence supports the recognition of cardiovascular disease as a potentially modifiable contributor to Alzheimer disease risk [9]. Hypertension, atherosclerosis, impaired vascular function, and other cardiovascular abnormalities may interact with neurodegenerative mechanisms and accelerate cognitive decline. Consequently, the prevention and management of cardiovascular disease may have implications beyond cardiovascular health and may contribute to strategies designed to preserve cognitive function during aging. Metabolic disorders, particularly obesity and diabetes mellitus, are also important potentially modifiable risk factors. Obesity is associated with impaired glucose regulation and increased susceptibility to type II diabetes. Persistent hyperglycemia may adversely affect neuronal function through several mechanisms, including metabolic stress, inflammatory activation, oxidative damage, and altered protein metabolism. Chronic disturbances in glucose homeostasis may promote the accumulation of beta-amyloid and contribute to neuroinflammatory processes, thereby increasing vulnerability to cognitive impairment [10]. Obesity may further intensify this risk through the release of pro-inflammatory cytokines and the development of systemic insulin resistance. These mechanisms demonstrate the close relationship between metabolic health and brain function and suggest that long-term disturbances in energy metabolism may influence neurodegenerative processes.

Several additional factors have been associated with an increased risk of developing Alzheimer disease. These include traumatic head injury, depression, smoking, cardiovascular and cerebrovascular disorders, elevated homocysteine concentrations, higher parental age at birth, and a family history of dementia. Traumatic brain injury may increase long-term neurological vulnerability through direct neuronal damage, inflammatory activation, and alterations in protein metabolism. Depression has also been associated with cognitive decline and may represent either a contributing risk factor or an early manifestation of neurodegenerative processes in some individuals. Smoking contributes to vascular injury and oxidative stress, while elevated homocysteine concentrations may adversely affect vascular and neuronal integrity. Genetic susceptibility is particularly important among individuals with a positive family history of Alzheimer disease. Having a first-degree relative with AD has been associated with an approximately 10% to 30% increase in the risk of developing the disorder. Individuals with two or more siblings affected by late-onset AD may have an approximately threefold higher risk than the general population [11][12][13]. The presence of the apolipoprotein E epsilon 4 allele represents one of the most extensively recognized genetic risk factors for late-onset Alzheimer disease. However, the presence of APOE ε4 does not independently determine that an individual will develop AD. Rather, it modifies susceptibility and interacts with other genetic, environmental, metabolic, and lifestyle-related factors. Despite the presence of several established risk factors, evidence also suggests that certain behavioral and lifestyle characteristics may contribute to reduced susceptibility or delayed cognitive decline. Higher educational attainment may support cognitive reserve and increase resilience against the clinical expression of neurodegenerative pathology. Engagement in intellectually stimulating leisure activities, including reading and playing musical instruments, may similarly contribute to the maintenance of cognitive function. Dietary patterns that support cardiovascular and metabolic health may indirectly reduce neurological risk by improving vascular function and glucose regulation. Regular aerobic exercise may provide additional benefits through improvements in cardiovascular fitness, cerebral circulation, metabolic regulation, and neurobiological function. Estrogen exposure in women and the use of anti-inflammatory agents have also been investigated as potential factors influencing disease risk. The etiology of Alzheimer disease should therefore be understood as the outcome of interacting biological and environmental influences rather than as a consequence of a single pathological event. Age and genetic susceptibility establish an important underlying level of risk, while cardiovascular disease, obesity, diabetes, smoking, head injury, metabolic dysfunction, and other exposures may further influence disease development and progression. Conversely, education, cognitive engagement, healthy dietary practices, physical activity, and effective cardiovascular and metabolic risk management may contribute to reducing potentially modifiable

components of risk. Continued investigation of these interacting factors remains essential for identifying individuals at increased risk and developing prevention strategies capable of delaying the onset or reducing the progression of Alzheimer disease.

Epidemiology

Alzheimer disease is predominantly associated with older age and represents a major and expanding global public health challenge. The increasing life expectancy of populations worldwide has contributed substantially to the growing number of individuals affected by Alzheimer disease and other forms of dementia. Globally, the prevalence of dementia increased from approximately 20.3 million individuals in 1990 to 43.8 million in 2016, representing an increase of approximately 116%. The burden continued to rise between 1990 and 2019, during which the incidence and prevalence of Alzheimer disease and other dementias increased by 147.95% and 160.84%, respectively. Current projections indicate that the global number of people living with dementia may reach approximately 150 million by 2050, representing a substantial increase compared with previous decades [14]. Age remains the strongest epidemiological determinant of Alzheimer disease. The incidence of AD increases markedly with advancing age and approximately doubles every five years after the age of 65. Annual incidence rates increase from less than 1% among individuals younger than 65 years to approximately 6% among those older than 85 years. Similarly, prevalence increases from approximately 10% after age 65 to nearly 40% among individuals aged 85 years and older. Women demonstrate slightly higher incidence rates than men, particularly after the age of 85 [15]. These epidemiological trends emphasize the close relationship between population aging and the increasing global burden of Alzheimer disease, highlighting the need for effective prevention, early detection, and long-term healthcare strategies.

Pathophysiology

Alzheimer disease is a progressive neurodegenerative disorder characterized by a complex interaction among abnormal protein processing, synaptic dysfunction, neuronal degeneration, neuroinflammation, and disruption of neurotransmitter systems. The pathological hallmarks of the disease include extracellular accumulation of abnormal neuritic amyloid plaques and intracellular neurofibrillary tangles, accompanied by progressive neuronal and synaptic loss. These abnormalities are particularly prominent in brain regions involved in memory and higher cognitive functions. Cholinergic neurons within the basal forebrain, including neurons associated with the nucleus basalis of Meynert, are especially vulnerable. Their degeneration contributes to impaired cholinergic neurotransmission and provides an important biological explanation for some of the cognitive manifestations observed in AD. The pathological process is not limited to a single molecular pathway. Instead, amyloid accumulation, tau-associated cytoskeletal disruption, impaired neurotransmission, inflammatory activation, oxidative stress, mitochondrial dysfunction, and neuronal death interact throughout disease progression [16]. The cholinergic hypothesis represents one of the earliest major explanations for the cognitive impairment associated with Alzheimer disease. This hypothesis proposes that progressive degeneration of cholinergic neurons produces a reduction in acetylcholine availability within cortical and hippocampal networks that support learning and memory. The early involvement of cholinergic neurons in the basal forebrain provided evidence for an important relationship between acetylcholine deficiency and cognitive dysfunction. Acetylcholine contributes to attention, learning, memory formation, synaptic plasticity, and other processes required for normal cognitive performance. Reduction of cholinergic signaling can therefore impair the functional capacity of neuronal networks even before extensive neuronal loss becomes clinically apparent. Amyloid beta may further aggravate cholinergic dysfunction by promoting cholinergic synaptic loss and reducing acetylcholine release. Clinical observations also support the importance of cholinergic signaling because medications with anticholinergic activity can impair memory and cognitive performance, particularly in older individuals [17]. This biological relationship contributed to the development of cholinesterase inhibitors as symptomatic treatments for AD, although restoration of cholinergic neurotransmission does not eliminate the underlying neurodegenerative process.

The amyloid hypothesis has become one of the central models for understanding the molecular pathogenesis of Alzheimer disease, particularly in genetically determined early-onset disease. Amyloid beta is generated from amyloid precursor protein through sequential proteolytic processing. APP is a transmembrane protein that undergoes cleavage through alternative enzymatic pathways. Under the non-amyloidogenic pathway, cleavage involving alpha-secretase prevents the formation of the amyloidogenic Aβ peptide. In contrast, sequential cleavage by beta-secretase followed by gamma-secretase produces amyloid beta peptides, including Aβ42 [18]. Aβ42 contains 42 amino acids and has a greater tendency to aggregate than shorter amyloid beta species. Increased production, reduced clearance, or altered processing of Aβ42 can therefore increase the concentration of aggregation-prone peptides within the brain. These peptides can assemble into oligomeric and fibrillar structures and eventually contribute to extracellular amyloid plaque formation. Soluble amyloid oligomers are also considered important mediators of synaptic dysfunction and neuronal injury because they can interfere with synaptic signaling before extensive plaque deposition occurs. Amyloid accumulation can initiate a cascade

of pathological events that extends beyond the direct toxicity of aggregated peptide. Abnormal amyloid beta can interfere with synaptic plasticity, alter neuronal membrane function, promote oxidative stress, activate microglia and astrocytes, and contribute to inflammatory signaling. Persistent activation of glial cells can produce inflammatory mediators that further damage neurons and synapses. Amyloid-related pathology can also interact with tau phosphorylation and aggregation, linking extracellular amyloid pathology with intracellular cytoskeletal abnormalities. Neurofibrillary tangles consist primarily of hyperphosphorylated tau protein. Under physiological conditions, tau stabilizes neuronal microtubules and supports axonal transport. Abnormal phosphorylation alters tau structure and reduces its ability to maintain microtubule integrity. Tau subsequently aggregates into paired helical filaments and neurofibrillary tangles, disrupting intracellular transport and contributing to neuronal degeneration. Thus, amyloid and tau pathology should not be regarded as completely independent processes. Their interaction forms part of a broader molecular cascade associated with progressive synaptic and neuronal dysfunction.

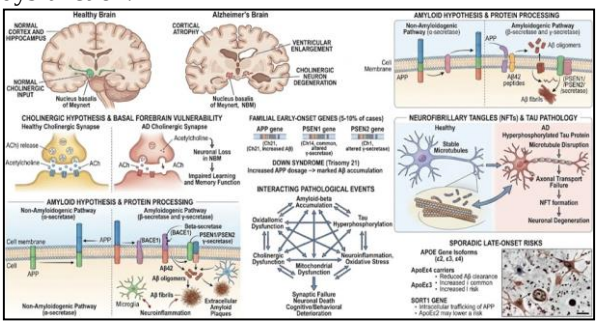

Figure-4: Pathophysiology of Alzheimer's Disease.

The genetic basis of Alzheimer disease provides further evidence supporting the importance of amyloid metabolism. Down syndrome is particularly relevant because it results from trisomy 21 and therefore produces an additional copy of genes located on chromosome 21, including the gene encoding amyloid precursor protein. Increased APP gene dosage can lead to increased availability of APP and greater production of amyloid beta peptides. Individuals with Down syndrome consequently have a markedly increased susceptibility to Alzheimer-type neuropathology. Approximately 40% to 80% of individuals with Down syndrome may develop clinical AD by the fifth or sixth decade of life, while nearly all affected individuals develop characteristic Alzheimer pathology, including amyloid plaques and neurofibrillary tangles [19]. This association provides important biological evidence that increased APP dosage can contribute to amyloid accumulation and subsequent neurodegeneration. A small proportion of Alzheimer disease cases arise from autosomal dominant genetic mutations with high penetrance. Familial early-onset Alzheimer disease has been associated primarily with pathogenic variants involving APP, presenilin 1, and presenilin 2. The APP gene is located on chromosome 21, whereas PSEN1 is located on chromosome 14 and PSEN2 is located on chromosome 1. APP mutations can alter APP processing and increase the production or accumulation of amyloid beta. Presenilin proteins form essential components of the gamma-secretase complex, and pathogenic variants in PSEN1 or PSEN2 can alter gamma-secretase activity and amyloid beta processing. These changes may increase the relative production of aggregation-prone Aβ42 and facilitate its accumulation within the brain. Although pathogenic mutations in APP, PSEN1, and PSEN2 account for only approximately 5% to 10% of Alzheimer disease cases, they have a strong association with early-onset familial disease. PSEN1 mutations represent the most common cause among these inherited forms and account for approximately 5% of all AD cases [20].

In contrast to rare autosomal dominant mutations, apolipoprotein E represents a major genetic modifier of susceptibility to late-onset Alzheimer disease. APOE encodes a protein involved in lipid transport and metabolism and has an important relationship with amyloid beta handling within the central nervous system. Three major APOE alleles are recognized, namely ε2, ε3, and ε4. The ε3 allele represents the most common form, whereas ε2 has generally been associated with lower AD risk and ε4 with increased susceptibility. The APOE ε4 allele is considered one of the most important genetic risk factors for sporadic late-onset Alzheimer disease [20]. Heterozygous carriers have an approximately threefold increased risk, while homozygous carriers may have an approximately fifteenfold increased risk of developing AD. The association may become more pronounced in early-onset disease among individuals carrying two ε4 alleles or among heterozygous carriers with a positive family history. The biological influence of APOE ε4 extends beyond simple genetic susceptibility. ApoE participates in lipid transport, membrane maintenance, synaptic function, and amyloid metabolism. Differences in ApoE isoforms can influence amyloid beta aggregation, clearance, and deposition, as well as inflammatory responses and neuronal repair mechanisms. The ε4 allele therefore may increase disease susceptibility through several interacting mechanisms rather than through a single pathological pathway. Importantly, APOE ε4 is a risk allele rather than a deterministic mutation. Many carriers do not develop Alzheimer disease, while individuals without the ε4 allele can develop the disorder. Disease expression therefore depends on interactions among genetic background, age, vascular factors, metabolic health, environmental exposures, and other molecular processes.

Additional genetic pathways involved in intracellular protein trafficking and lipid metabolism have also been implicated in Alzheimer disease. Variants in SORT1, which encodes the sortilin receptor, have been identified in familial and sporadic forms of AD [11]. Sortilin contributes to intracellular trafficking and participates in the transport of APP between cellular compartments, including pathways involving the cell surface and the Golgi-endoplasmic reticulum system. Alterations in this trafficking machinery may influence APP localization, processing, and degradation and could consequently modify amyloid beta production or clearance. Such findings reinforce the concept that Alzheimer disease results from disturbances in several interconnected cellular systems rather than from amyloid accumulation alone. The contemporary pathophysiological model of Alzheimer disease therefore integrates amyloid processing, tau pathology, cholinergic dysfunction, genetic susceptibility, lipid metabolism, neuroinflammation, and progressive neuronal loss. Amyloid beta accumulation may represent an initiating or amplifying event in genetically determined disease, while tau pathology provides a closer relationship with neuronal degeneration and clinical disease progression. Cholinergic dysfunction contributes to cognitive symptoms and remains an important therapeutic target for symptomatic treatment. Genetic abnormalities involving APP, PSEN1, and PSEN2 can produce highly penetrant early-onset disease, whereas APOE ε4 modifies susceptibility to late-onset disease. SORT1 and other genes further demonstrate the importance of intracellular trafficking and protein metabolism. Together, these mechanisms produce progressive synaptic failure, neuronal dysfunction, and neuronal death, ultimately leading to the cognitive, behavioral, and functional deterioration characteristic of Alzheimer disease [11][16][17][18][19][20].

Histopathology

The histopathological profile of Alzheimer disease is defined by a combination of abnormal extracellular protein deposition, intracellular cytoskeletal pathology, synaptic loss, and progressive neuronal degeneration. These changes develop within characteristic anatomical patterns and provide the structural basis for the clinical manifestations of the disease. Three major pathological features are traditionally recognized in AD, namely neuritic plaques, neurofibrillary tangles, and cortical neuronal degeneration [21]. Although these lesions are central to the pathological diagnosis of Alzheimer disease, their relationship with cognitive impairment is not equivalent. In particular, the distribution and burden of tau-associated neurofibrillary pathology and synaptic degeneration demonstrate stronger relationships with clinical severity than the absolute number of amyloid plaques. The histopathological examination of AD therefore requires assessment of both amyloid and tau pathology together with neuronal and synaptic alterations. Neuritic plaques represent one of the characteristic microscopic abnormalities of Alzheimer disease. These lesions are generally spherical structures consisting of an extracellular accumulation of amyloid beta peptide surrounded by dystrophic and enlarged neuronal processes. Amyloid beta deposits may occur within cortical gray matter and around meningeal and cerebral blood vessels. Within the cerebral cortex, amyloid deposition often appears as multiple microscopic foci that can enlarge and coalesce into plaque-like structures. The central amyloid material may become surrounded by damaged axonal and dendritic processes, activated microglia, and reactive astrocytes, reflecting a local tissue response to persistent protein accumulation. The distribution and composition of amyloid deposits vary among patients and may also change according to the stage of disease.

The presence of amyloid plaques alone does not establish the presence of clinical Alzheimer dementia. Amyloid deposition can occur in individuals who remain cognitively intact, particularly with increasing age. Conversely, some individuals diagnosed clinically with dementia may demonstrate relatively limited plaque deposition on brain imaging or pathological examination. This observation indicates that amyloid accumulation represents an important component of AD pathology but does not independently determine the degree of cognitive dysfunction. The biological consequences of amyloid may depend on its molecular form, anatomical distribution, interaction with tau, effects on synaptic function, and capacity to induce inflammatory and neuronal responses. Soluble amyloid oligomers may also exert biological effects before mature plaques become established, making the relationship between visible plaque burden and neuronal dysfunction more complex than a direct dose-response association. Neurofibrillary tangles constitute the second major histopathological feature of Alzheimer disease and are composed predominantly of abnormal tau protein within neurons. Under physiological conditions, tau is a microtubule-associated protein that contributes to the stabilization and organization of microtubules within neuronal axons. Microtubules provide structural pathways required for the intracellular transport of proteins, organelles, and other cellular components. Tau therefore contributes to the maintenance of axonal architecture and efficient neuronal transport. In AD, pathological alterations in tau include excessive phosphorylation, conformational changes, misfolding, and aggregation. These modifications impair tau function and promote the formation of paired helical filaments that subsequently accumulate within neuronal cytoplasm as neurofibrillary tangles.

The development of neurofibrillary pathology is closely associated with neuronal dysfunction and degeneration. Abnormal tau can

detach from microtubules, resulting in impaired microtubule stability and disruption of axonal transport. Progressive accumulation of aggregated tau can further compromise cellular function and contribute to neuronal death. Neurofibrillary tangles characteristically emerge within the hippocampal formation and related medial temporal structures before extending into additional areas of the cerebral cortex. This anatomical progression corresponds to the evolution of cognitive impairment because the hippocampus and associated cortical regions are essential for memory formation and retrieval. As tau pathology spreads into cortical regions involved in language, executive function, visuospatial processing, and behavioral regulation, the clinical phenotype becomes increasingly extensive. Cortical neuronal degeneration represents the third major component of AD histopathology. Progressive loss of neurons occurs throughout affected brain regions and is accompanied by substantial synaptic degeneration. One characteristic microscopic abnormality is granulovacuolar degeneration within hippocampal pyramidal neurons. This lesion consists of cytoplasmic vacuoles containing dense granules and is particularly associated with neuronal populations vulnerable to Alzheimer pathology. However, neuronal death alone does not completely explain the degree of cognitive deterioration. Synaptic dysfunction and loss occur early in the disease process and may substantially impair communication between surviving neurons before widespread neuronal loss becomes apparent.

Presynaptic terminals, including boutons arising from cortical pyramidal neurons, are particularly important indicators of functional neuronal integrity. Reduction in the density of presynaptic boutons within specific cortical layers, especially laminae III and IV, has been associated with cognitive impairment. This relationship suggests that loss of functional synaptic connections may have a greater influence on cognitive performance than the absolute number of amyloid plaques. The brain can tolerate some degree of pathological protein accumulation without immediate clinical dementia, whereas disruption of neuronal connectivity directly interferes with information processing. Consequently, synaptic degeneration provides an important structural link between microscopic pathology and the progressive impairment of memory, reasoning, attention, and executive function. The Braak and Braak staging system provides a framework for describing the anatomical progression of neurofibrillary pathology in Alzheimer disease. This system divides the distribution of neurofibrillary tangles into six stages according to the regions affected and the extent of pathological spread. Early stages predominantly involve the transentorhinal and entorhinal regions, followed by increasing involvement of the hippocampal formation and associated temporal structures. Later stages involve broader areas of the neocortex. The progression described by Braak and Braak provides a useful pathological model for understanding the relationship between tau distribution and the clinical evolution of AD. The staging system has become an important component of neuropathological assessment and has contributed to the pathological criteria used in the evaluation of Alzheimer disease. The burden of neurofibrillary tangles generally demonstrates a stronger relationship with dementia severity than the quantity of amyloid plaques [22]. This observation is clinically important because it indicates that tau pathology more closely reflects the extent of neuronal injury and cognitive deterioration. Amyloid deposition remains an important defining pathological feature of AD and helps distinguish Alzheimer pathology from several other neurodegenerative disorders. However, the spatial distribution and progression of tau pathology provide greater information regarding the severity of neurodegeneration. This distinction has influenced current biomarker research, particularly the increasing emphasis on tau imaging and cerebrospinal fluid and plasma phosphorylated tau measurements [25][26][27].

The relationship between amyloid and tau pathology has traditionally been conceptualized using a model in which amyloid initiates or facilitates a pathological cascade, whereas tau pathology contributes directly to neuronal dysfunction and degeneration [23]. Although this model simplifies a complex biological process, it provides a useful framework for understanding the complementary roles of the two proteins. Amyloid beta accumulation may alter synaptic function, activate glial cells, promote inflammatory signaling, and facilitate pathological changes in tau. Abnormal tau then becomes increasingly associated with cytoskeletal disruption, impaired axonal transport, synaptic failure, and neuronal death. Current evidence indicates that these processes interact with other mechanisms, including neuroinflammation, vascular dysfunction, oxidative stress, mitochondrial abnormalities, and impaired protein clearance. Amyloid beta accumulation can also occur within cerebral blood vessels, producing cerebral amyloid angiopathy. Although Aβ40 is generally more abundant than Aβ42 in many amyloid deposits, both species can contribute to pathological accumulation. In cerebral amyloid angiopathy, amyloid material is deposited within the walls of small- and medium-sized cerebral vessels. This vascular deposition can compromise vessel integrity and cerebral microvascular function. CAA frequently occurs in association with Alzheimer pathology and has clinical relevance because its presence has been associated with greater cognitive impairment and potentially more rapid cognitive decline [24]. Vascular amyloid pathology can therefore contribute to the

neurological consequences of AD through mechanisms that extend beyond parenchymal plaque formation. Vascular pathology also contributes to the clinical expression and progression of dementia. Although the precise relationship between cerebrovascular disease and neurodegenerative pathology remains incompletely defined, vascular lesions can reduce the brain's capacity to tolerate Alzheimer-related neuronal injury. Subcortical infarcts, for example, have been associated with an approximately fourfold increase in the risk of dementia. Cerebrovascular disease may also increase the severity of cognitive impairment and accelerate clinical progression [25][26][27]. Vascular injury can impair cerebral perfusion, disrupt white matter integrity, damage neuronal networks, and reduce cognitive reserve. When cerebrovascular lesions occur alongside amyloid and tau pathology, their effects may be additive or interactive. Overall, the histopathology of Alzheimer disease reflects a progressive interaction among amyloid deposition, tau aggregation, synaptic dysfunction, neuronal degeneration, and vascular abnormalities. Neuritic plaques provide an important pathological signature of amyloid accumulation, while neurofibrillary tangles reflect the progressive intracellular aggregation of abnormal tau. Cortical and hippocampal neuronal degeneration, together with loss of presynaptic connections, provides a closer structural basis for cognitive decline. The Braak and Braak staging system demonstrates the ordered anatomical progression of tau pathology, while cerebral amyloid angiopathy and cerebrovascular disease illustrate the contribution of vascular mechanisms. These findings support a multidimensional pathological model in which amyloid accumulation, tau propagation, synaptic failure, neuroinflammation, neuronal loss, and vascular injury interact to produce the progressive clinical phenotype of Alzheimer disease.

History and Physical

A comprehensive history and physical examination are fundamental components of the clinical assessment of Alzheimer disease. Because patients may have limited awareness of their cognitive impairment, information from family members and caregivers is often essential. The assessment should establish the onset, pattern, progression, and functional consequences of cognitive changes, including memory, behavior, judgment, language, and executive abilities. Evaluation of basic activities of daily living and instrumental activities of daily living provides important information regarding disease severity. IADLs, including shopping, financial management, meal preparation, tax-related tasks, and housekeeping, require greater cognitive and organizational capacity and may become impaired during earlier stages of disease. Medication history should also be reviewed, particularly exposure to anticholinergic agents that may worsen cognitive performance. Social history should include alcohol consumption and previous or current use of illicit substances because these factors may contribute to cognitive impairment [28]. Physical assessment should include a complete neurological examination and mental status evaluation to determine disease stage and identify alternative causes of cognitive decline. Neurological findings are often relatively preserved during early AD, although anosmia may occur. In advanced disease, patients may develop aphasia, apraxia, primitive reflexes, frontal release signs, and progressive loss of responsiveness. Cognitive screening should assess attention, concentration, recent and remote memory, language, visuospatial ability, praxis, and executive function. The Montreal Cognitive Assessment is preferred for detecting mild cognitive impairment because it is more sensitive than the MMSE [29][30]. The Mini-Cog, combining clock drawing with three-item recall, provides another useful screening approach and is relatively independent of educational attainment [31]. Serial mental status assessments remain essential for monitoring progression and neuropsychiatric manifestations.

Evaluation

The evaluation of suspected Alzheimer disease requires a structured clinical approach that integrates history, cognitive assessment, laboratory investigation, neuroimaging, and, when indicated, disease-specific biomarkers. Initial assessment should establish the medical and family history and identify medications that may cause or aggravate cognitive impairment. Bedside cognitive screening using the MMSE or, preferably, the MoCA can provide an initial assessment of cognitive performance. Routine laboratory investigations do not demonstrate a specific biochemical abnormality in AD but are important for excluding potentially reversible causes of cognitive decline. Common investigations include a complete blood count, comprehensive metabolic panel, thyroid-stimulating hormone, and vitamin B12 concentrations [32][33][34].

Structural neuroimaging supports the evaluation by identifying cerebral atrophy and excluding alternative neurological disorders. CT may demonstrate cerebral atrophy and enlargement of the third ventricle, although these findings are nonspecific. MRI provides greater structural resolution and may demonstrate characteristic atrophy involving the entorhinal cortex, medial temporal regions, and hippocampi. It also assists in identifying patterns suggestive of other neurodegenerative disorders, including frontotemporal lobar degeneration, multisystem atrophy, Creutzfeldt-Jakob disease, and progressive supranuclear palsy [35]. Volumetric MRI can quantify hippocampal and medial temporal lobe atrophy, although interpretation remains challenging because similar changes occur during normal aging [36]. Functional imaging provides complementary information. FDG-PET can identify regional cerebral metabolic abnormalities associated with early or

preclinical AD [37][38]. Amyloid PET permits in vivo visualization of cerebral Aβ deposition, although amyloid positivity can also occur in cognitively normal older adults [38]. CSF biomarkers provide biochemical evidence of AD pathology, with reduced Aβ42 and increased p-tau and t-tau concentrations. The Aβ42/40 ratio can improve diagnostic accuracy for amyloid pathology [39]. Neuropsychological assessment remains valuable for identifying mild cognitive impairment, while genetic testing is generally reserved for selected families with suspected early-onset inherited disease. MCI represents an intermediate state between normal aging and dementia, and many affected individuals progress to dementia within 5 to 7 years [4].

Treatment / Management

Management of Alzheimer disease involves a combination of symptomatic pharmacotherapy, disease-modifying treatment, management of behavioral and psychological manifestations, and nonpharmacological interventions. Historically, no treatment could eliminate the underlying neurodegenerative process, and symptomatic therapy remained the principal clinical approach [40][41][42]. Cholinesterase inhibitors, including donepezil, rivastigmine, and galantamine, increase acetylcholine availability within neuronal synapses and may provide modest benefits in cognition and daily functioning [43][44][45]. Donepezil is commonly used across the mild-to-severe stages, while rivastigmine can be administered orally or transdermally and is used in mild disease and selected MCI cases. Galantamine is generally used during mild stages. Gastrointestinal effects such as nausea, vomiting, and diarrhea are common, while increased vagal activity may produce bradycardia, conduction abnormalities, or syncope. Memantine is a partial NMDA receptor antagonist approved for moderate-to-severe AD. By reducing excessive NMDA receptor-mediated calcium influx, it may limit excitotoxic neuronal injury. Dizziness, headache, constipation, and generalized discomfort may occur. Memantine can be administered alone or combined with a cholinesterase inhibitor, particularly during moderate-to-severe disease [46]. Disease-modifying therapy has introduced a therapeutic approach directed toward amyloid pathology rather than symptom control. Monoclonal antibodies targeting amyloid beta include aducanumab, lecanemab, and donanemab. Aducanumab demonstrated amyloid reduction but failed to consistently demonstrate clinical benefit in its pivotal trials [47][48]. Lecanemab demonstrated amyloid reduction and approximately 27% slowing of clinical progression in a phase III trial [49]. Donanemab also reduced amyloid burden and demonstrated slowing of cognitive decline [50]. Amyloid-targeting therapy may produce amyloid-related imaging abnormalities, including ARIA-E and ARIA-H, with APOE ε4 carriage and cerebral amyloid angiopathy increasing risk [51]. Management should also address depression, anxiety, psychosis, agitation, sleep disturbance, and caregiver burden. Nonpharmacological approaches should generally precede antipsychotic treatment. Safe surroundings, structured routines, exercise, sunlight exposure, reassurance, redirection, and attention to comfort can reduce behavioral symptoms. Antipsychotics require cautious use because of cerebrovascular and mortality risks, while benzodiazepines may worsen agitation and delirium. Brexpiprazole was approved for agitation associated with AD dementia [52]. Regular aerobic exercise may support functional capacity and slow disease progression. Treatment should remain individualized and continued only when meaningful benefit outweighs adverse effects.

Conclusion:

Alzheimer disease is a progressive neurodegenerative disorder resulting from interactions among genetic susceptibility, abnormal amyloid and tau metabolism, synaptic dysfunction, neuronal degeneration, neuroinflammation, and vascular pathology. Its increasing prevalence with population aging creates a substantial clinical and healthcare burden. Accurate evaluation requires integration of clinical history, cognitive assessment, laboratory investigations, neuroimaging, and disease-specific biomarkers. Cholinesterase inhibitors and memantine remain important symptomatic treatments, while amyloid-targeting monoclonal antibodies have introduced disease-modifying approaches for selected patients. Continued research into molecular mechanisms, biomarkers, prevention strategies, and therapeutic targets remains essential for improving early diagnosis, slowing disease progression, and preserving cognitive and functional independence.

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