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Exploring the Multiple Pathogenic Mechanisms, Clinical Manifestations, Diagnostic and Therapeutic Dilemmas, and Research Frontiers of Alzheimer's Disease

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Abstract. With the rapid growth of the global aging population, the incidence of Alzheimer's disease (AD) has been increasing year by year. This progressive, irreversible and insidious neurodegenerative disease will lead to progressive cognitive deterioration, posing a major public health threat to seniors and bringing heavy burdens to families and society. However, its complex and multi-dimensional pathogenesis has not been fully clarified, and major bottlenecks still exist in early screening, accurate diagnosis, and radical treatment. This paper systematically reviews the progression of AD, categorizing it into three stages: the subjective cognitive decline, mild cognitive impairment and AD dementia and describes its progression from early latent symptoms to severe functional impairment in middle and late stages. Based on this, this article deeply analyzes the multiple and interrelated pathogenic mechanisms of AD from four dimensions: canonical amyloid-tau proteinopathy, cerebral metabolic dysfunction, cerebral white matter structural impairment and systemic inducing factors. The study summarizes current mainstream interventions, pointing out key dilemmas including delayed diagnosis, single-target therapeutic limitations, and comorbidity interference, and lack of curative drugs. Additionally, this paper reviews cutting-edge research fields: diabetes-associated pathological pathways, DTI imaging, AI-assisted diagnosis, gut-brain axis regulation, and new targeted treatments. The study shows that AD is a complex disease driven by multiple factors, systems and mechanisms, and a single intervention is difficult to overcome the current predicament. This paper offers a comprehensive theoretical reference for AD early warning, pathological mechanism research, precision diagnosis and treatment, and translational medical development.

Keywords: Alzheimer's disease, neurodegenerative disease, pathogenesis, frontier research

1. Introduction

Global population aging continuously drives the annual upward trend in the global incidence of Alzheimer's disease(AD). Between 2000 and 2019, the number of deaths reported from AD increased by more than 145% [1]. The estimated numbers of patients with AD dementia, prodromal AD and preclinical AD globally are 32 million, 69 million and 315 million respectively. The total of these three groups amounts to 416 million in the Alzheimer's disease spectrum, accounting for 22%

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of individuals aged 50 years and older [2]. As an irreversible neurodegenerative disorder with insidious early onset and high disabling risk, Alzheimer's disease places overwhelming caregiving and financial pressure on affected families and imposes a heavy cost burden on public health services globally. According to statistics, total spending on healthcare, long-term care and hospice services for adults aged 65 and older living with dementia was estimated at 360 billion dollars in 2024 [3]. These epidemiological data fully reflect the global public health crisis brought by AD.

Currently, AD has a complex multifactorial etiology. No approved disease-modifying therapeutics are available and unified criteria for early screening remain absent in routine clinical practice. Based on these unaddressed challenges, this review adopts systematic literature retrieval and multi-dimensional comparative analysis as core research methods. This manuscript intends to stratify AD into three clinical phases: subjective cognitive decline, mild cognitive impairment and AD dementia to summarize its symptomatic progression. It further aims to elucidate AD's multifactorial pathogenesis from four core categories: canonical amyloid-tau proteinopathy, cerebral metabolic dysfunction, cerebral white matter structural damage and systemic predisposing comorbidities. Meanwhile, it summarizes prevailing clinical interventions and auxiliary diagnostic strategies, identifies core clinical obstacles such as delayed diagnosis, limitations of single-target therapy and interference from concomitant illnesses, and catalogues frontier hotspots including DTI-based early neuroimaging, AI-assisted screening, gut-brain axis modulation and novel targeted pharmacology. This review is designed to lay solid theoretical foundations for future AD early warning, exploration, precision clinical management and translational medicine advancement.

2. Clinical characteristics and disease progression

The progression of AD follows a staged pattern with distinct clinical manifestations at every phase. This part first defines AD as a degenerative disease of the central nervous system, then elaborates three successive stages including SCD, MCI and AD dementia, and ends with a generalized summary of its evolving clinical traits.

2.1. The definition of Alzheimer's disease

AD is an irreversible progressive neurodegenerative disorder that impairs both mental and non-mental functions [4]. Continuous cerebral deposition of toxic Aβ and tau proteins triggers gradual neuronal loss and widespread disruption of neural circuits, leading to irreversible and persistent cognitive decline, which also constitutes the fundamental cause of disease deterioration. Different from transient cognitive impairment caused by cerebrovascular lesions and metabolic disorders, AD features a progressive and long-term degenerative process that slowly impairs patients' cognitive functions and Activities of Daily Living (ADL) over several years without spontaneous remission. Standard symptomatic treatments cannot reverse its damage, and no curative therapies are available, setting it apart from reversible cognitive disorders.

2.2. Ultra-early stage, early stage(MCI), moderate and advanced stage

Subjective cognitive decline (SCD) is the ultra-early stage of AD without quantitative objective pathology indicators. Patients only feel subjective memory decline, such as frequently forgetting recent events and having a slower reaction. However, standard neuropsychological assessments as well as imaging examinations fail to capture definite abnormal lesions at this time. All daily life practices of the patients can be completed independently. Longitudinal cohort data shows that

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approximately 10% of individuals with SCD progress to MCI each year. Most patients take these mild abnormal feelings for natural aging, thus missing the best window for early screening and intervention.

Mild cognitive impairment (MCI) corresponds to the symptomatic early stage of AD. This stage is marked by impairment in one or more cognitive domains, observable both subjectively and objectively. Nevertheless, such deterioration does not impair the individual's capacity to complete daily activities on their own [5]. Patients show mild impairment in memory and attention, and subtle obstacles emerge in complex daily tasks. Imaging examinations can detect slight brain microstructural injuries linked to abnormal protein clearance. At this stage, cerebral Aβ deposition is markedly higher than that in the subjective cognitive decline phase, with the overall deposition level tending to stabilize. The involvement of tau pathology expands further and spreads to the lateral cerebral cortex. Biomarker-positive MCI patients carry an annual conversion risk of 15%-20% to clinical dementia.

In dementia periods, patients face comprehensive cognitive collapse, severe time-and-place deterioration and obvious personality changes. Massive irreversible neuronal damage makes patients lose the ability to take care of themselves entirely. They need round-the-clock supervision in daily routines, and are highly susceptible to concurrent complications including falls, malnutrition and mental behavioral abnormalities. Typical behavioral manifestations cover sundowning agitation, aimless wandering, repetitive stereotyped movements, paranoid delusions of property theft, unprovoked verbal or physical aggression, persistent apathy and complete loss of interest in daily activities.

3. The multiple pathogenesis

AD arises from a complex interplay of multiple pathological cascades rather than a single cause, forming the multifaceted basis of its progressive neurodegeneration. These mechanisms, ranging from core cerebral proteinopathies to systemic metabolic and microbial influences, collectively drive the initiation and progression of AD pathology, as detailed in the following sections. Impaired white matter microstructures disrupt glymphatic fluid transport and block the clearance of aggregated Aβ and tau peptides, creating a vicious cycle that amplifies intracellular protein pathology and accelerates neuronal damage.

3.1. Classic protein pathological mechanisms

AD is characterized by two closely linked abnormal protein pathways: amyloid-beta (Aβ) deposition and tau protein hyperphosphorylation. Soluble Aβ peptides, produced via sequential cleavage of amyloid-beta precursor protein (APP), misfold and aggregate to form extracellular senile plaques, triggering neurotoxic cascades including oxidative stress, neuroinflammation and synaptic dysfunction. Progressive deposition of amyloid-beta peptides induces tau hyperphosphorylation, followed by the formation of neurofibrillary tangles that lead to neurodegeneration and cerebral atrophy [6]. These two pathological alterations jointly induce extensive neuronal apoptosis, disrupt neural signal transduction, and cause the progressive loss of functional neural circuits. Even low concentrations of oligomeric Aβ, the most toxic subtype, can suppress hippocampal long-term potentiation and worsen synaptic impairment, neuronal oxidative damage and excessive microglial activation long before visible extracellular plaque deposits emerge in preclinical AD.

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3.2. Mechanism of brain metabolic abnormalities

Recent studies have advanced a new conceptual framework of AD as "type 3 diabetes", underscoring the central contributions of cerebral insulin resistance and impaired glucose metabolism in the pathogenesis of the disease [7]. In the early stage of the disease, the brain develops insulin resistance, manifested by reduced insulin receptor sensitivity and impaired glucose transporter function, leading to markedly decreased cerebral glucose levels. Disordered insulin signaling not only impairs neuronal energy supply but also exacerbates amyloid-beta (Aβ) and tau pathology, accelerating synaptic damage, dendritic spine loss, and early neuronal degeneration. This persistent metabolic deficiency further sensitizes brain tissues to protein aggregation and neuroinflammation, creating a self-reinforcing pathological cycle that hastens disease progression. This metabolic dysfunction typically precedes overt cognitive symptoms, serving as a key preclinical biomarker of AD progress.

However, this hypothesis is still subject to academic disputes. Some researchers hold that cerebral insulin resistance is a secondary result of Aβ deposition rather than the primary trigger of AD. Other clinical studies also fail to confirm a direct causal link between peripheral glucose disorders and dementia risk, while supporters attribute these inconsistent findings to age, cardiovascular complications and different disease phases.

3.3. Mechanism of brain structural damage

Advanced neuroimaging techniques, particularly diffusion tensor imaging (DTI), have confirmed that extensive white matter abnormalities occur in AD patients even in early symptomatic stages. Multilevel analyses of DTI reveal that AD patients exhibit extensive microstructural damage, structural disconnection and topological abnormalities in the corpus callosum, fornix, and medial temporal lobe, including the hippocampus and cingulum [8]. These microstructural injuries disrupt the integrity of long-range brain networks, impairing interregional communication between cortical and subcortical regions. This neural disconnection is closely associated with cognitive impairment, including impaired memory consolidation, executive function and attention regulation. Such white matter degradation further hinders glymphatic fluid transport, generating a vicious cycle that amplifies protein clearance defects.

3.4. Systemic triggering mechanisms

Multiple systemic mechanisms act as key modifiers of AD pathogenesis, linking peripheral health to central neurodegeneration. Type 2 diabetes mellitus (T2DM) and AD share common pathological pathways, with key mediators including glycogen synthase kinase-3β (GSK-3β) and dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A). GSK3β is one of the major tau kinases responsible for the hyperphosphorylation and aggregation of tau protein [9]. DYRK1A has been shown to promote Aβ aggregation and tau phosphorylation, leading to neurofibrillary tangle (NFT) formation and neurodegeneration. Accordingly, DYRK1A inhibition represents a potential therapeutic approach for AD [10]. Chronic systemic inflammation, characterized by elevated pro-inflammatory cytokines, and persistent oxidative stress further exacerbate neuronal injury and Aβ aggregation. Additionally, gut microbiota dysbiosis disrupts the gut-brain axis, altering systemic metabolite profiles as well as neuroinflammatory signaling. Peripheral inflammatory molecules and microbial metabolites are capable of crossing the blood-brain barrier to activate microglia, which

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subsequently secrete pro-inflammatory cytokines and aggravate intracellular protein pathological alterations. These cascades disturb cerebral homeostasis and accelerate the progression of AD.

4. Current mainstream clinical treatments and interventions

AD management currently relies on a combination of symptomatic pharmacotherapy, non-pharmacological interventions, and auxiliary diagnostic strategies, each playing a distinct role in alleviating symptoms, slowing progression, and facilitating early disease detection.

4.1. Pharmacological interventions

Currently approved medications for AD primarily target neurotransmitter imbalances to mitigate cognitive and functional symptoms. Cholinesterase inhibitors, such as donepezil and rivastigmine, work by inhibiting acetylcholine breakdown, temporarily enhancing cholinergic neurotransmission to improve memory and attention in mild-to-moderate AD patients. Memantine, an NMDA receptor antagonist, modulates glutamatergic overstimulation to reduce excitotoxic neuronal damage, offering modest benefits for moderate-to-severe cases. In addition, sleep-targeted pharmacotherapies have shown preliminary therapeutic effects in AD-related sleep disturbances. Suvorexant has been shown to markedly prolong total sleep duration and improve sleep efficiency, while decreasing wake after sleep onset [11]. However, these drugs only provide symptomatic relief. They fail to target the underlying Aβ and tau pathologies, nor can they reverse established neuronal damage or halt disease progression. Consequently, their transient clinical benefits gradually wane with prolonged treatment, whereas newly developed anti-Aβ monoclonal antibodies like lecanemab can clear amyloid plaques and delay early cognitive impairment matching the aforementioned amyloid pathology, with tau-targeted small molecules also undergoing clinical trials to block tau aggregation.

4.2. Non-pharmacological interventions

As complementary strategies to pharmacotherapy, non-pharmacological interventions focus on maintaining functional capacity and slowing cognitive decline. Structured cognitive training, including memory and problem-solving exercises, helps preserve neural plasticity and activate brain compensatory mechanisms. Social engagement, such as group activities and community participation, reduces isolation and enhances emotional well-being, indirectly mitigating cognitive deterioration. Lifestyle modifications, including a balanced diet, regular physical activity, and adequate sleep, can improve cerebral perfusion and reduce systemic metabolic risk factors. Aerobic exercise promotes brain-derived neurotrophic factor (BDNF) secretion, clears cerebral Aβ deposition via lymphatic circulation and suppresses neuroinflammation. The Mediterranean diet rich in omega-3 fatty acids, polyphenols and antioxidants alleviates brain insulin resistance and inhibits tau hyperphosphorylation, exerting long-term neuroprotective effects. Additionally, optimal management of comorbid conditions like diabetes and hypertension prevents vascular contributions to neurodegeneration, thereby slowing AD-related functional decline.

4.3. Auxiliary diagnostic interventions

Auxiliary diagnostic intervention is conducive to the early detection and monitoring of the disease. Neuropsychological assessments, such as the MMSE and MoCA, provide standardized evaluations of cognitive domains, enabling early identification of subtle cognitive impairments and tracking disease progression. Advanced neuroimaging technology, particularly diffusion tensor imaging

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(DTI), detects microstructural white matter damage in key regions like the hippocampus and corpus callosum before overt symptoms appear, serving as a preclinical biomarker for AD. A quantitative DTI-derived metric, named the analysis along the perivascular space (ALPS) index, is applied to non-invasively assess glymphatic clearance function. Lower values indicate impaired interstitial fluid drainage and weakened clearance ability of neurotoxic proteins including Aβ and tau. The ALPS index shows a progressive decline across distinct clinical stages (SCD: 1.51±0.08; MCI: 1.37±0.13; AD: 1.32±0.14; P=0.001) and correlates with Aβ-PET, tau-PET and FDG-PET scores [12]. These diagnostic tools enable timely intervention and formulate personalized regimens, improving patients' long-term prognostic outcomes.

5. Core bottlenecks in clinical diagnosis and treatment of AD

AD is difficult to cure completely for multiple and complex reasons. Three interrelated core limitations stand out: delayed early screening, diagnostic confusion caused by its complex multifactorial etiology and comorbidities, and the absence of curative therapeutic drugs. These overlapping barriers greatly delay early diagnosis and effective intervention, worsening patient prognosis.

5.1. Insidious disease onset and deficiencies in early screening

AD progresses insidiously, with irreversible brain pathology building up decades before overt cognitive symptoms emerge. Easy, low-cost screening methods are lacking for patients in preclinical SCD and MCI stages. Conventional diagnostic examinations, including cerebrospinal fluid testing and advanced neuroimaging, have clear drawbacks: lumbar puncture is invasive, whereas PET and DTI scans cost too much to be widely applied in mass screening at primary care facilities. Consequently, most patients are only diagnosed at moderate or advanced dementia stages. By then, massive neuronal loss, white matter disconnection and severe cerebral atrophy have occurred, the best therapeutic window is largely closed, and neural circuits become irreparable.

5.2. Complex pathological cascades and comorbidity interference

AD is driven by a tangled network of multiple pathological cascades rather than a single pathogenic factor. Beyond the core Aβ deposition and tau hyperphosphorylation protein lesions, impaired glymphatic circulation, widespread white matter microstructural damage, systemic metabolic dysfunction and gut microbiota dysbiosis all jointly facilitate the initiation and continuous deterioration of brain pathology. Common comorbidities including type 2 diabetes mellitus and cerebrovascular disorders will independently induce central neuroinflammation and abnormal toxic protein aggregation inside the brain, creating highly overlapping clinical manifestations that disturb clinicians' differential diagnosis between pure AD and mixed cognitive impairment. Furthermore, therapeutic regimens designed to target only a single pathological pathway fail to suppress the parallel damage from multiple pathogenic mechanisms, thereby resulting in limited treatment efficacy.

5.3. Major barriers to disease-modifying drug development

AD's intricate, multi-layered multifactorial pathogenesis creates massive technical barriers to the research and development of disease-modifying drugs. All drugs currently approved for clinical use only temporarily relieve superficial symptoms such as memory loss, executive dysfunction and

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neuropsychiatric disturbances, yet they cannot reverse progressive neuronal injury, halt sustained toxic protein aggregation or repair disrupted long-range brain neural circuits. Up to now, no curative therapy that reverses AD's full disease trajectory has been developed. These three interconnected clinical bottlenecks mutually exacerbate one another, highlighting the urgent need to explore affordable high-sensitivity early biomarkers and innovative multi-target combined intervention strategies for translational AD research.

6. Conclusion

This paper systematically elaborates the multi-layered interconnected pathogenesis of AD and three major clinical bottlenecks hindering accurate diagnosis and effective clinical intervention. It illustrates the core dual protein pathological cascades: mutual Aβ aggregation and tau hyperphosphorylation jointly trigger sustained neurotoxic responses, and toxic soluble Aβ oligomers impair synaptic plasticity at the preclinical SCD and MCI stages, prior to the onset of overt dementia symptoms. Supported by abundant DTI neuroimaging evidence, widespread white matter lesions disrupt long-distance brain network integrity and block glymphatic fluid clearance, forming a vicious cycle of toxic protein accumulation inside cerebral tissue. It further analyzes peripheral regulatory pathways, where type 2 diabetes, chronic inflammation and gut microbiota imbalance aggravate central neurodegeneration through the gut-brain axis, with GSK3β and DYRK1A as core kinases connecting metabolic dysfunction to interacted lesions.

Three prominent clinical dilemmas are summarized: insidious onset limits large-scale early screening, intertwined pathology and comorbidities disturb differential diagnosis, and approved drugs only relieve superficial cognitive symptoms instead of reversing neuronal loss. Five frontier research hotspots address these barriers: shared targets for diabetes-AD comorbidity, DTI-assisted non-invasive diagnosis, AI multi-modal identification models, gut microbiota intervention, and targeted therapy for GSK3β and DYRK1A. As a pure literature review, this study lacks original cellular or clinical experimental data to validate relevant molecular mechanisms. Overall, this paper identifies AD as a systemic degenerative disorder with central-peripheral pathological crosstalk, stressing low-cost non-invasive early screening and multi-target treatment as core strategies to resolve existing clinical limitations.

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