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Mini Review

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Unlock the Code for the Diagnosis and Treatment of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia worldwide. Characterized by cognitive decline, behavioral changes, and impaired daily functioning, AD's complex pathology-including amyloid-beta (Aβ) plaques and tau neurofibrillary tangles-has hindered accurate diagnosis and effective treatment. This mini review discusses current diagnostic advancements and therapeutic interventions aimed at addressing these challenges. Diagnostic strategies for AD have evolved, combining clinical assessments with neuroimaging, cerebrospinal fluid (CSF) biomarkers, blood-based biomarkers, and genetic testing to distinguish AD from other dementias. Treatment approaches, although unable to cure the disease, now include recently approved anti-amyloid monoclonal antibodies such as lecanemab and donanemab, which target disease progression. Alongside pharmacologic treatments like cholinesterase inhibitors and N-Methyl-D-Aspartate (NMDA) receptor antagonists, non-pharmacologic interventions (e.g., cognitive therapy and physical exercise) help manage symptoms and enhance quality of life. Emerging research in tau-targeted therapies, gene therapy, and precision medicine holds promise for more effective, tailored approaches. Continued exploration into AD's pathophysiology may unlock transformative treatments, offering new hope for patients and their caregivers.

Keywords

Alzheimer's, Cerebrospinal fluid, Dementia, Brain, Diagnosis

Introduction

AD is a progressive neurodegenerative disorder characterized by cognitive decline, behavioral changes, and functional impairment. As the most common cause of dementia worldwide, AD poses significant challenges for diagnosis and treatment due to its complex pathophysiology, overlapping symptoms with other dementias, and limited therapeutic options. This review provides an overview of current diagnostic approaches and treatment modalities for AD.

The primary neuropathological hallmarks of AD include the accumulation of extracellular Aβ plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau proteins. These protein aggregates contribute to neuronal death, synaptic dysfunction, and neuroinflammation, resulting in brain atrophy, particularly in the hippocampus and cortex, which are essential for memory and cognitive functions. In AD, several brain regions are affected as the disease progresses. The primary impacted regions include the hippocampus, entorhinal cortex, posterior cingulate cortex, and parietal and temporal lobes. These areas are crucial for memory, navigation, and higher cognitive functions. Neuroimaging in AD, especially with magnetic resonance imaging (MRI) and positron emission

tomography (PET) scans, reveals early atrophy in the hippocampus and entorhinal cortex, hypometabolism in the posterior cingulate cortex and later stage atrophy in the parietal and temporal lobes. Clinically, AD presents as gradual memory loss, particularly of recent events, alongside impairments in reasoning, language, and visuospatial abilities. As the disease progresses, behavioral symptoms such as agitation, depression, and psychosis often emerge, further complicating patient care and management.

Diagnosis of AD

The diagnosis of AD can be difficult given its insidious onset. In fact, studies show that up to 40% of AD patients were never told by their primary care physician that they had AD [1]. In 2018, the Alzheimer's Association released the first clinical practice guidelines for the evaluation of cognitive impairment suspected to be a result of AD and related dementias in both primary care and specialty care settings, which was revised recently to reflect the advancement in biomarker development and neuroimaging [2]. The primary recommendation, however, was still that all middle-aged or older individuals who self-report or for whom their care partner reports cognitive, behavioral, or functional changes undergo a timely multitiered evaluation. Although a definitive diagnosis traditionally would require autopsy, physicians can now diagnose AD with a high degree of accuracy using the following methods.

Clinical assessment

The first step in AD diagnosis involves a thorough clinical history and neuropsychological evaluation to assess affected cognitive domains. Standardized cognitive tests, such as the Mini-Mental State Examination or the Montreal Cognitive Assessment, are commonly used to evaluate cognitive decline and identify memory deficits, with the former being shorter of the two and the latter being more sensitive to visual-spatial issues.

Neuroimaging studies

MRI, as a structural imaging, helps visualize brain atrophy patterns associated with AD. Functional imaging, such as PET scans using amyloid or tau tracers, allows direct visualization of protein aggregates, and markedly improve diagnostic accuracy.

Biomarkers

CSF biomarkers, including Aβ42, total tau, and phosphorylated tau, are reliable indicators of AD pathology. More recently blood-based biomarkers are becoming the tool of choice due to their non-invasive, cost-effective nature of screening.

Genetic testing

While genetic testing is not typically routine for sporadic AD, identifying mutations in genes like APOE ε4, presenilin-1, and presenilin-2 can aid in diagnosing early-onset familial AD.

The constellation of cognitive assessments, neuroimaging, and biomarker analyses underscores diagnostic accuracy, enabling providers to distinguish AD from other dementias, such as frontotemporal dementia and vascular dementia (Figure 1).

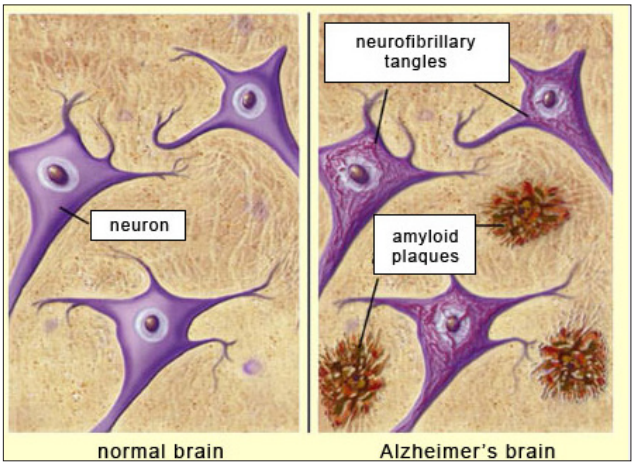


Figure 1: Diagram of the neuropathological changes in AD, highlighting amyloid plaques, neurofibrillary tangles, and the resulting neuronal damage in the brain [3].

Treatment of AD

While there is no cure for AD, treatments primarily focus on symptom management and slowing disease progression.

Pharmacologic treatments

Cholinesterase inhibitors

These drugs, including donepezil, rivastigmine, and galantamine, inhibit the breakdown of acetylcholine, a neurotransmitter critical for memory and learning. Although cholinesterase inhibitors do not alter disease progression, they can modestly improve cognitive and behavioral symptoms, with the approved efficacy over 12 - 18 months on average.

NMDA receptor antagonists

Memantine is an NMDA receptor antagonist that helps regulate glutamate activity, reducing excitotoxicity associated with neuronal damage. Memantine is typically prescribed for more advanced cases and either taken along or combined with cholinesterase inhibitors.

Anti-amyloid therapies

Recently, therapies targeting amyloid plaques have gained attention. Aducanumab, an anti-amyloid antibody, received FDA approval in 2021, making it the first disease-modifying treatment aimed at reducing amyloid plaque accumulation. As its clinical efficacy and safety were debated, there were two additional monoclonal antibody drugs, lecanemab (Leqembi) and donanemab (Kisunla), received full approval from the FDA in 2024. They are administered intravenously to attack the amyloid plaques and bind to them. As monoclonal antibodies, they enable the body to remove them effectively.

Anti-tau therapies

Tau targeted therapies, such as tau aggregation inhibitors, are in the clinical trial stages, with promising results in

Table 1: Summary of current pharmacologic and non-pharmacologic treatments for AD [4].

Therapeutic approach	Agent	Effect
Cholinesterase inhibitors	Donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne)	Enhances cognition and delays symptom progression
NMDA receptor antagonists	Memantine (Nemanda)	Improves cognition and reduces excitotoxicity
Anti-amyloid therapies	Lecanemab (Leqembi) and donanemab (Kisunla)	Reduces amyloid plaques and potential disease modifier
Anti-tau therapies	Experimental (e.g., tau aggregation inhibitors)	Reduces tau pathology (in trial phase)
Non-pharmacologic	CBT, physical exercise, and social activities	Manage symptoms and improve quality of life

preclinical studies. These therapies aim to prevent tau protein hyperphosphorylation and reduce neurofibrillary tangle formation.

Non-pharmacologic interventions

Non-pharmacologic approaches play a vital role in managing AD symptoms and enhancing the quality of life. Interventions may include cognitive behavioral therapy (CBT), physical exercise, and social engagement activities designed to stimulate cognitive function aside from the addition of the Mediterranean diet and water consumption. Additionally, support groups and counseling can aid caregivers, who often experience high levels of stress while managing AD patients (Table 1).

Research into AD pathophysiology has opened new avenues for potential treatments targeting underlying mechanisms. One promising area is gene therapy, focusing on correcting or silencing AD-related gene mutations, is under investigation. Precision medicine approaches, tailoring treatment based on individual genetic and biomarker profiles, could further enhance the efficacy of AD therapies [5].

Conclusion

AD remains a formidable challenge due to its complex pathology and limited interventional options. Although current therapies provide symptomatic relief, disease-modifying treatments are still refined. The future of AD treatment lies in a multidisciplinary approach combining pharmacologic and non-pharmacologic treatments with emerging targeted therapies. Continuous research undermines its molecular mechanisms and encourages the development of novel diagnostic tools for more effective strategies.

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None.

Conflict of Interest

None.

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