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Alzheimer's Disease: Advances in Early Diagnosis and Emerging Therapeutics

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Abstract: Alzheimer's disease is a chronic, progressive neurodegenerative disorder marked by cognitive decline, behavioral changes, and eventual loss of independent function. It is the leading cause of dementia globally, posing a significant social, economic, and medical burden. Recent scientific breakthroughs have shifted the focus from symptomatic treatment to early diagnosis and disease-modifying interventions. This review explores the molecular pathogenesis of AD, advances in early diagnostic techniques including novel biomarkers and neuroimaging, and emerging therapeutics ranging from monoclonal antibodies to gene therapy and lifestyle interventions. By integrating early detection strategies with emerging therapeutics, we move closer to intercepting AD at its earliest and most manageable stage.

Keywords: *Alzheimer's, Neurological Loss, MRI, Antibodies, Personalized Medicines.*

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I. INTRODUCTION

Alzheimer's disease affects an estimated 55 million individuals globally, with the number expected to surpass 150 million by 2050. Aging remains the single most significant risk factor, although genetics and lifestyle also contribute. Historically, AD diagnosis occurs at the dementia stage, when significant neuronal loss has already occurred. Recent efforts have been directed toward identifying the disease in its preclinical phase – years or even decades before symptoms appear - allowing the potential for earlier intervention.

II. PATHOPHYSIOLOGY

AD is a multifactorial disease with complex molecular and cellular mechanisms:

➢ *Amloid Cascade Hypothesis*

- Central to AD pathogenesis is the accumulation of amyloid – beta (Aβ) peptides particularly, Aβ42, which aggregate into extracellular plagues
- Aβ is derived from the amyloid precursor protein (APPP) via sequential cleavage by β secretase (BACE1) and γ secretase.
- Oligomeric forms of Aβ are particularly neurotoxic, impairing synaptic function and initiating inflammatory responses.

➢ *Tau Pathology*

- Intracellular hyperphosphorylation of tau protein disrupts microtubule stabilization, leading to the formation of neurofibrillary tangles (NFTs).
- Tau spreads in a prion – like manner from affected to healthy neurons, correlating more closely with cognitive decline than Aβ burden

➢ *Neuro Inflammation*

- Microglial activation plays a dual role: initially clearly amyloid, but chronically activated microglia releases pro-inflammatory cytokines and ROS.
- TREM2, a microglial receptor, has emerged as a genetic risk factor, and its variants influence immune responses to amyloid.

➢ *Other Mechanisms*

- Oxidative stress, mitochondrial dysfunction, insulin resistance in the brain (type 3 diabetes), and vascular dysregulation are increasingly recognized as contributory.
- Synaptic dysfunction, not just neuronal loss, plays a pivotal role in early symptoms.

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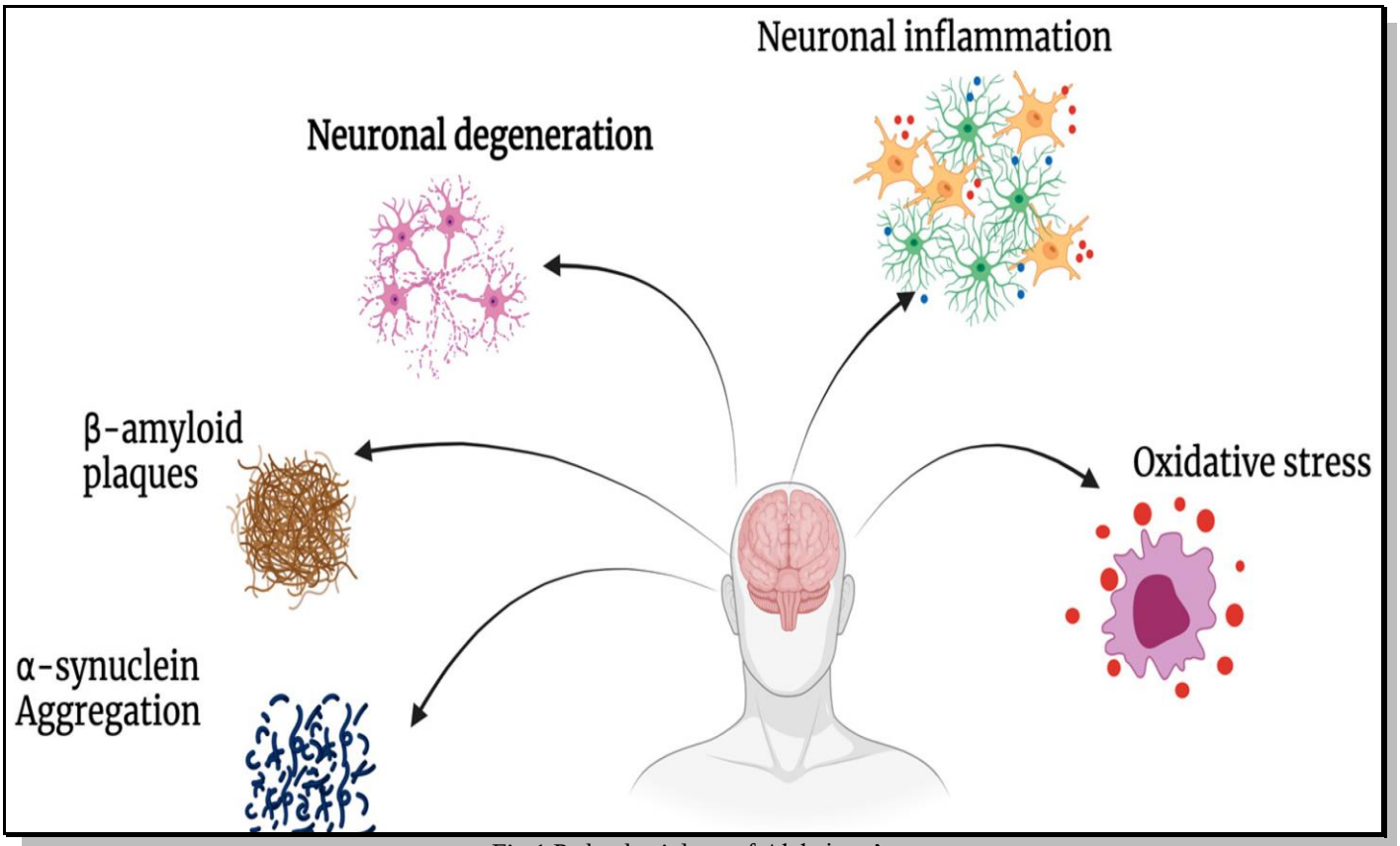

Fig 1 Pathophysiology of Alzheimer's

III. ADVANCES IN EARLY DIAGNOSIS

Early and accurate diagnosis is critical for intervention and clinical trial enrollment. Diagnosis now spans clinical assessment, cognitive testing, biomarkers, imaging, and genetics.

A. Fluid Biomarkers

➢ *Cerebrospinal Fluid (CSF)*

- Decreased Aβ42 and Aβ42/Aβ40 ratio: early amyloid deposition.
- Increased total tau (t-tau): reflects neuronal damage.
- Phosphorylated tau (p-tau 181, p-tau217): specific for tau pathology.
- Newer makers include NfL, YKL-40, and neurogranin, indicating axonal injury and synaptic dysfunction.

➢ *Blood -Based Biomarkers*

- Plasma p-tau 181 and p-217: highly specific and correlate with CSF levels and PET imaging.
- Neurofilament light chain (NfL): a marker of neurodegeneration.
- Glial fibrillary acidic proteins (GFAP): reflets astrocytic activation.
- These are easier to implement in clinical settings and may soon enable mass screening.

B. NeuroImaging

➢ *Structural Imaging (MRI)*

- Atrophy in hippocampus, entorhinal cortex, and posterior cingulate.
- Used to rule out alternative causes of dementia (e.g., vascular, tumor).

➢ *Functional Imaging (FDG- PET)*

- Decreased glucose metabolism in temporospatial and posterior cingulate regions.

➢ *Molecular Imaging*

- Amyloid -PET (e.g., Florbetapir, Florbetaben): detects fibrillar Aβ
- Tau-PET (e.g., Flortaucipir): identifies NFT distribution.
- Limitations: expensive and not widely available, but highly specific.

C. Digital and AI-Based Diagnostics

- Wearables and smartphones are being tested for detecting early cognitive changes through passive monitoring (e.g., speech, gait).
- AI models trained on neuroimaging and electronic health records can predict conversion from MCI to AD.

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D. Genetic Risk Assessment

➢ *Monogenic (Familial) ADIn*

- Mutations in APP,PSEN1,PSEN2 cause early -onset AD.
- Represent <1% of cases but crucial for understanding pathophysiology.

➢ *Polygenic (Sporadic) AD*

- APOE e4 allele: dose -dependent risk factor for late-onset AD.
- GWAS studies have identified .30 risk loci: CLU, PICALM, BIN1, TREM2, etc.
- Polygenic risk scores (PRS) integrate multiple variants to stratify individual risk.

IV. EMERGING THERAPEUTICS

Efforts are now focused on disease modification rather than symptomatic relief.

A. Amyloid-Targeting Therapies

➢ *Monoclonal Antibodies*

- Aducanumab (Biogen): targets aggregated Aβ; FDA approved in 2021amid controversy.
- Lecanemab (Eisai/Biogen): binds protofibrils; shown to modestly slow cognitive decline.
- Donanemab (Eli Lilly): targets modified Aβ; positive results in early AD

➢ *Other Approach.*

- BACE inhibitors (e.g., verubecestat): failed due to toxicity or lack of efficacy.
- γ -secretase modulators: more selective, in deployment.

B. Tau – Directed Therapies

- Antibodies (e.g., Semorinemab, Gosuranemab): target extracellular tau, mixed results so far.
- Kinase inhibitors: prevent tau hyperphosphorylation (e.g., GSK3β inhibitors).
- Tau aggregation inhibitors (eg., LMTX): in clinical trials.

C. Anti-Inflammatory and Neuroprotective Agents

- Microglial modulators (eg., TREM2 agonist).
- NSAIDs and TNF inhibitors have failed or shown limited efficacy.
- Neurotrophins mimetics (e.g., BDNF agonists) are under exploration.

D. Cholinergic and Glutamatergic Modulation

- Existing drugs (donepezil, rivastigmine) enhances cholinergic signaling.
- NMDA receptor antagonist (memantine) is used in moderate-to-severe AD.
- Newer agents target α7-nicotinic receptors or mGluRs.

E. Gene and RNA-Based Therapy

- Antisense oligonucleotides (ASOs) are being trialed to downregulate tau and APP.
- CRISPR-Cas9 gene editing in preclinical models to correct pathogenic mutations.
- AAV vectors are used for gene delivery in animal models.

F. Lifestyle and Multimodal Interventions

➢ *The Finger Trial (Finish Geriatric Intervention Study)*

- First large-scale trial showing cognitive benefit from a multidomain intervention:

✓ Diet
✓ Exercise
✓ Cognitive training
✓ Vascular risk monitoring

G. Current Challenges and Future Perspectives

- Diagnosis vs Prognosis: How to translate biomarker positivity into actionable steps for asymptomatic individuals.
- Therapeutic Window: Most DMT s work best early; need to identify and treat preclinical cases.
- Access and Cost: PET imaging and new therapies are costly and not universally accessible.
- Personalized Medicine: Need for tailoring therapy based on individual biomarkers, genetics, and comorbidities.
- Clinical Trial Design: Trails need to be longer, better stratified, and incorporate biomarkers as endpoints.

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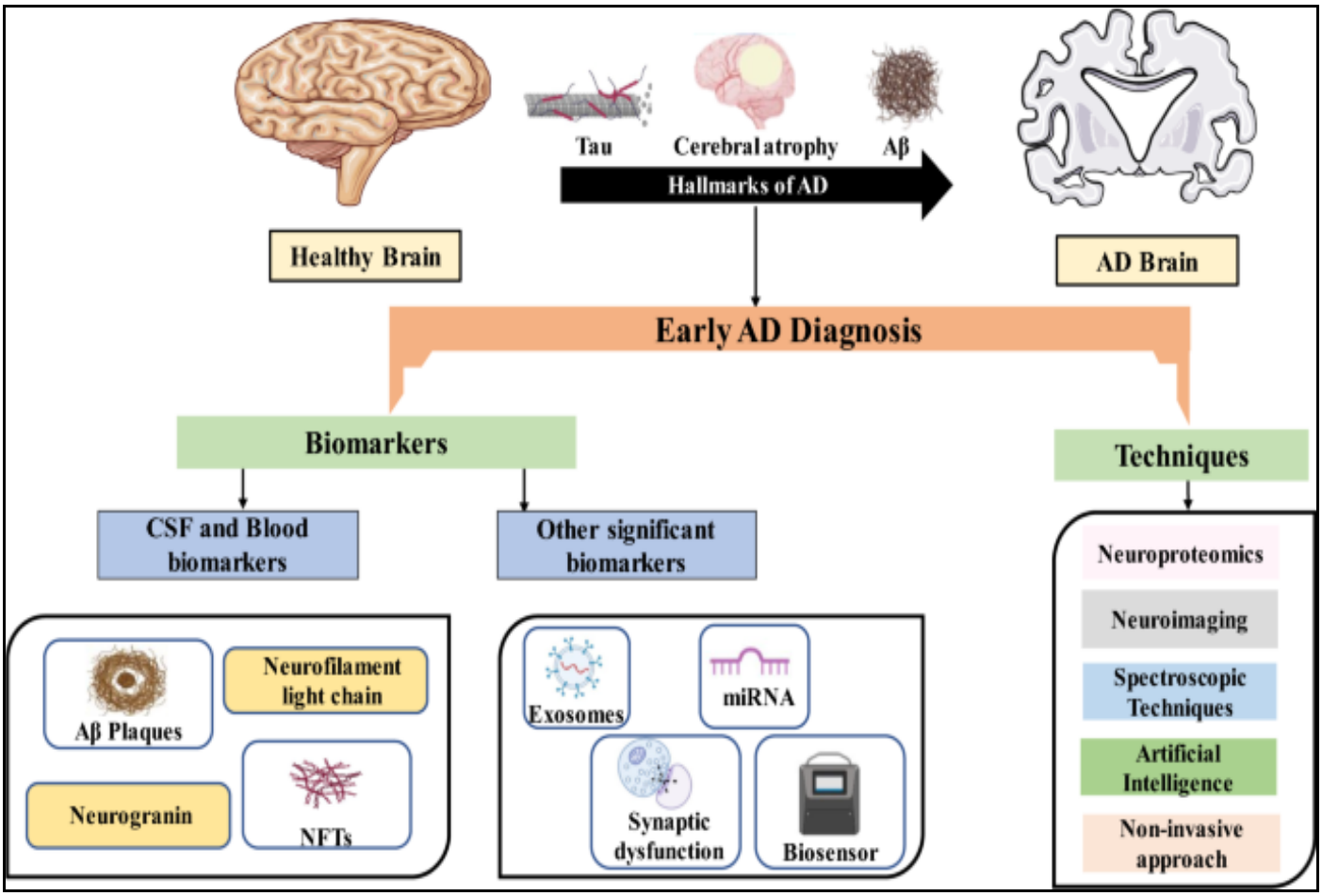

Fig 2 Advanced Early Diagnosis

V. CONCLUSION

The field of Alzheimer's research is undergoing a paradigm shift- from late-stage symptomatic management to early diagnosis and disease modification. Biomarker- based diagnostics, supported by AI and genetic profiling, are revolutionizing how we detect and stage the disease. At the same time, novel therapies, particularly immunotherapies targeting amyloid and tau, are showing the first signs of clinical benefit. While challenges remain, a future in which AD is detected early and progression halted is increasingly within reach.

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