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NOVEL INSIGHTS INTO ALZHEIMER'S DISEASE: A COMPREHENSIVE REVIEW

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ABSTRACT

This review synthesizes current evidence on the molecular and cellular underpinnings of AD and how these mechanisms translate to clinical symptoms, emphasizing the dynamic interplay between biomarkers and clinical phenotypes. Advances in diagnostic frameworks, including the 2018 updates from the National Institute on Aging–Alzheimer's Association (NIA-AA), now incorporate fluid biomarkers, neuroimaging, and preclinical staging, refining early detection strategies. Emerging disease-modifying therapies, particularly those targeting amyloid and tau pathways, offer cautious optimism despite ongoing challenges in efficacy and accessibility. Since Alois Alzheimer's first report in 1906, our understanding of AD has evolved significantly, revealing a multifaceted pathophysiological landscape that extends beyond classical β-amyloid (Aβ) plaques and neurofibrillary tangles (NFTs). Recent research highlights the roles of synaptic dysfunction, neuroinflammation, tau propagation, mitochondrial impairment, and disrupted proteostasis in the disease's onset and progression. Moreover, genetic risk factors—most notably *APOE ε4* and other variants uncovered by genome-wide association studies (GWAS)—have been linked to distinct pathogenic cascades. By consolidating and disseminating up-to-date, open-access scientific knowledge, we aim to support equitable education for clinicians and researchers navigating the complexities of Alzheimer's disease in a rapidly evolving therapeutic landscape.

KEYWORDS: Alzheimer's disease; neurodegeneration, diagnosis; history; medicine, neurodegeneration; pathophysiology, stages of AD, strategies.

INTRODUCTION

Alzheimer's disease (AD), named after the German psychiatrist Alois Alzheimer, is the most prevalent form of dementia. It is defined as a gradually progressive neurodegenerative disorder characterized by neuritic plaques and neurofibrillary tangles (see Figure 1), resulting from the accumulation of amyloid-beta peptide (Aβ) in the brain's most affected regions, specifically the medial temporal lobe and neocortical structures.[1]

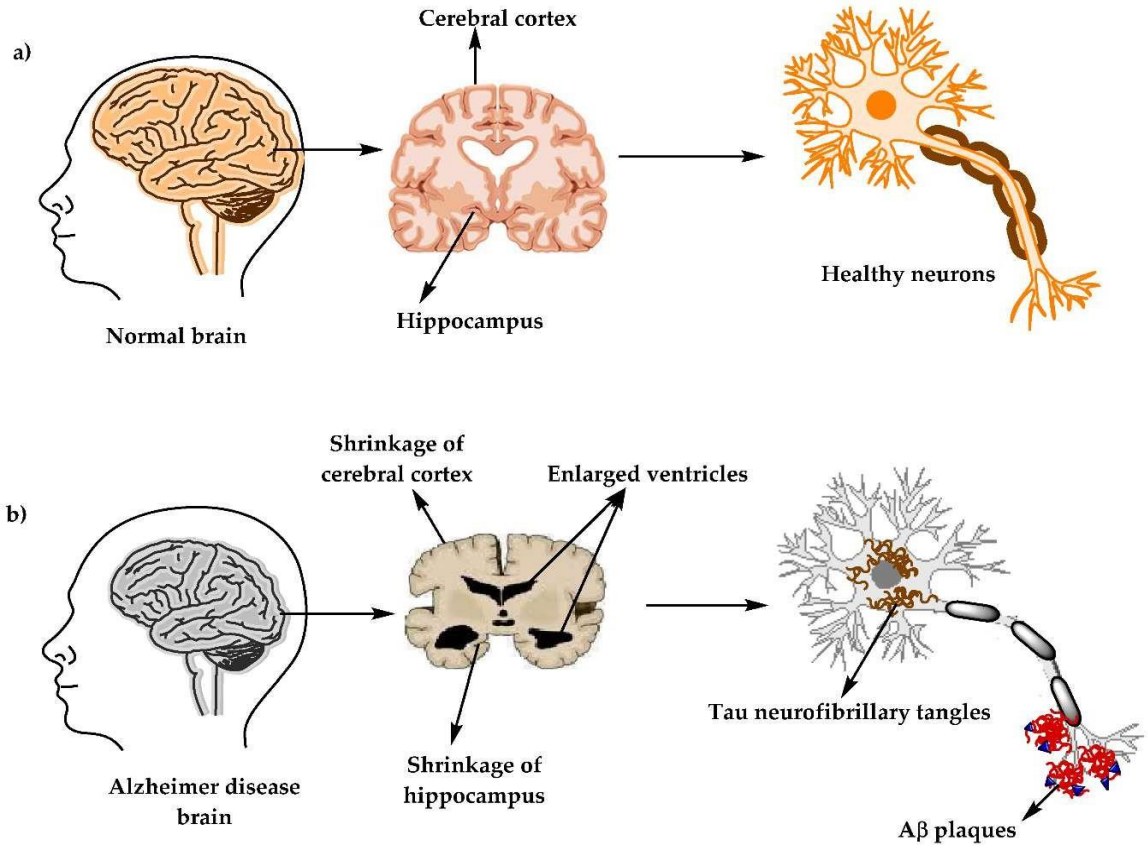
Alois Alzheimer observed amyloid plaques and significant neuronal loss while studying the brain of his first patient, who experienced memory loss and personality changes prior to death. He characterized this condition as a severe disease affecting the cerebral cortex. Emil Kraepelin was the first to refer to this medical condition as Alzheimer's disease in the 8th edition of his psychiatry handbook.[2]

The progressive decline in cognitive abilities can be attributed to cerebral disorders such as Alzheimer's disease (AD) or other factors, including intoxications, infections, abnormalities in the pulmonary and circulatory systems that lead to decreased oxygen supply to the brain, nutritional deficiencies, vitamin B12 deficiency, tumors, and more conditions.[4]

Dementia represents a significant global health issue, impacting around 55.2 million individuals, as reported by the World Health Organization in 2022.[5]

Prevalence differs by region for those aged over 60: 2.9% in Southeast Asia, 6.5% in Europe, and between 3.1% and 5.7% in other regions. Although the overall incidence is on the rise, some high-income nations are experiencing a decrease.

By the year 2030, the number of individuals with dementia is projected to reach 78 million, with worldwide care costs surpassing US$ 2.8 trillion, significantly affecting both individuals and communities.[7]



AIM

To comprehensively review the current understanding of Alzheimer's disease, including its pathophysiology, clinical features, risk factors, diagnostic approaches, biomarkers, therapeutic strategies, and the emerging role of artificial intelligence in improving early diagnosis and disease management.

MAIN REVIEW

Neuropathological vision in Alzheimer's disease

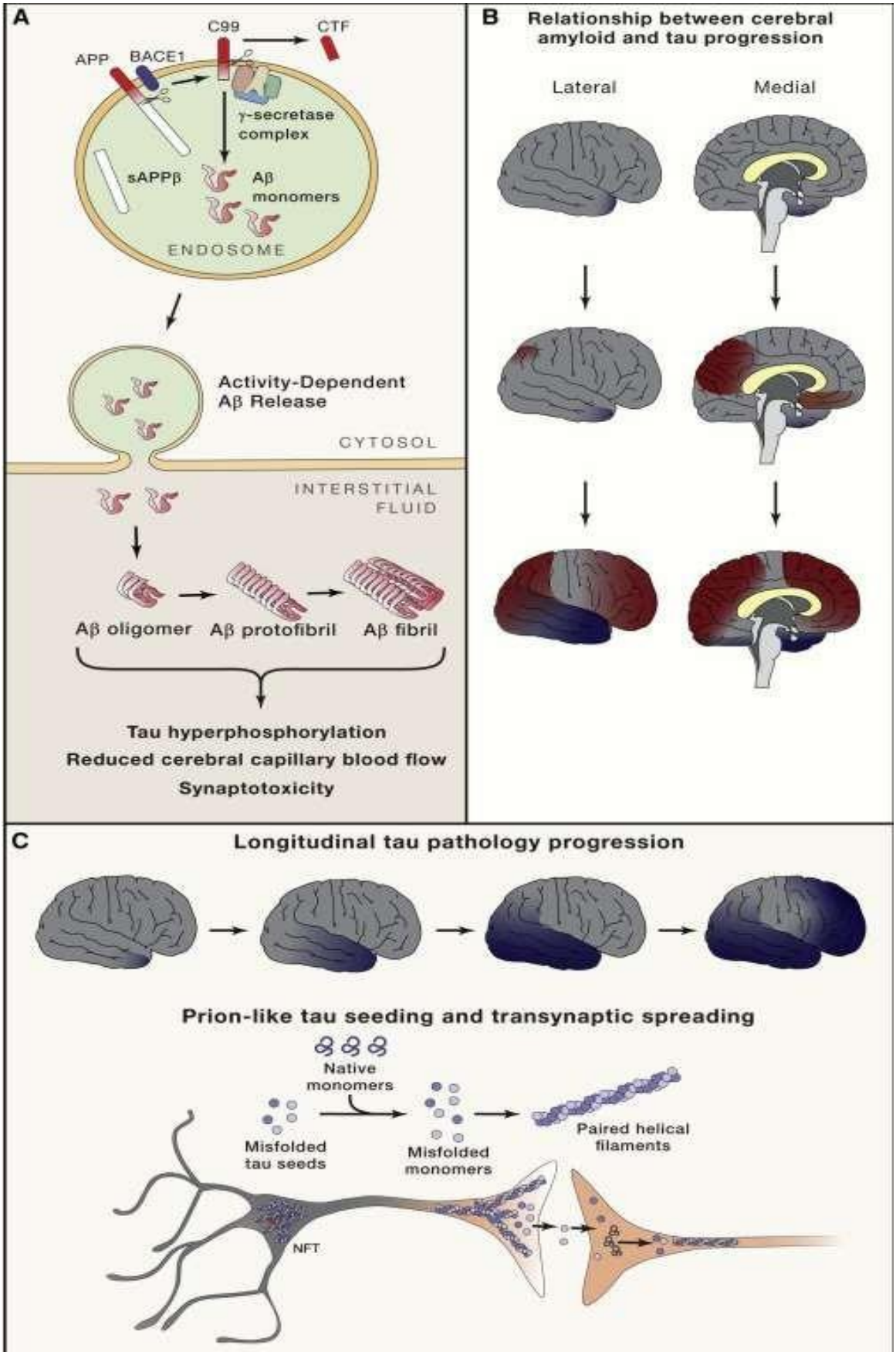
The Aβ peptide was initially recognized as the key component of meningovascular amyloid in 1984 (Glenner and Wong, 1984) and later identified as the primary element in amyloid neuritic plaques (Masters et al., 1985). In the decades that followed, extensive research was conducted to elucidate the fundamental biology of this peptide and its involvement in the pathophysiology of Alzheimer's disease (AD). Aβ is generated through the sequential cleavage of β-amyloid precursor protein (APP) by β-secretase and γ-secretase (Figure 2A; for a review, see Haass et al. [2012]). The β-secretase enzyme (BACE1) cleaves APP at the N-terminus of the Aβ sequence, resulting in the release of secreted APP-β and the membrane-bound C99 fragment (Vassar et al., 1999).[8]

The γ-secretase complex is composed of four protein subunits: presenilin (PSEN), presenilin enhancer (PEN), APH, and Nicastrin. There are various isoforms of PSEN (PSEN1/PSEN2) and APH (APHA, APH B/C); up to four distinct γ-secretase complexes may be present within a single cell (Voytyuk et al., 2018; Xia, 2019). After cleavage by BACE1, the γ-secretase complex attaches to the N-terminally cleaved APP fragment (C99) and intramembranously cleaves at the ε-site, releasing the C-terminal fragment (CTF) and Aβ48. The γ-secretase complex then continues processing along the remaining Aβ C-terminal end, sequentially producing shorter peptides until the Aβ peptide is liberated from the complex (typically after generating peptides of 38-, 40-, and 42-amino acids in length).[9]

The recent publication of high-resolution substrate-enzyme cryogenic electron microscopy (cryo-EM) molecular structures for the γ-secretase-APP C83 fragment and the γ-secretase-Notch 100 fragment (Yang et al., 2019; Zhou et al., 2019) has conclusively identified substrate binding sites for γ-secretase and provides compelling evidence for a helix-unwinding model of sequential substrate processing.[10]

BACE1, γ-secretase, and APP assemble into a large molecular complex in vivo, indicating that Aβ production may be enhanced by the direct shuttling of APP between the two processing enzymes (Liu et al., 2019). Aβ is produced predominantly in endosomes, and its release from neurons is modulated by synaptic activity.[11]

Aβ is produced predominantly in endosomes, and its release from neurons is modulated by synaptic activity (Kamenetz et al., 2003, Wei et al., 2010) both pre-synaptically (Cirrito et al., 2005, Cirrito et al., 2008) and post-synaptically (Verges et al., 2011).


A
C99
CTF
APP
BACE1
γ-secretase complex
sAPPβ
Aβ monomers
ENDOSOME
Activity-Dependent Aβ Release
CYTOSOL
INTERSTITIAL FLUID
Aβ oligomer
Aβ protofibril
Aβ fibril
Tau hyperphosphorylation
Reduced cerebral capillary blood flow
Synaptotoxicity
B
Relationship between cerebral amyloid and tau progression
Lateral
Medial
C
Longitudinal tau pathology progression
Prion-like tau seeding and transynaptic spreading
Native monomers
Misfolded tau seeds
Misfolded monomers
Paired helical filaments
NFT

Symptoms

Memory loss is the primary indicator of Alzheimer's disease. In the early stages, individuals may struggle to recall recent events or discussions. As the disease progresses, memory deterioration intensifies, accompanied by additional symptoms.[12]

Initially, a person affected by the disease might recognize their difficulties with memory and clarity of thought. As the symptoms worsen, it is often a family member or friend who observes these changes more readily. The alterations in the brain caused by Alzheimer's disease result in symptoms that progressively worsen over time.[13]

Memory

While everyone experiences memory lapses occasionally, the memory impairment associated with Alzheimer's disease is persistent. As time passes, this memory loss impacts the ability to function effectively both at work and at home.[14]

Individuals with Alzheimer's disease may

- Repeat questions and statements multiple times.
- Forget conversations, appointments, or events.
- Misplace items, often placing them in illogical locations.
- Become disoriented in familiar surroundings.
- Forget the names of relatives and common objects.
- Struggle to find the appropriate words, articulate thoughts, or engage in conversations**.**

Thinking and reasoning

Alzheimer's disease impairs concentration and cognitive processes, particularly regarding abstract ideas like numbers. Managing multiple tasks simultaneously becomes particularly challenging.

Individuals may find it difficult to handle finances, reconcile checkbooks, and pay bills. Eventually, those with Alzheimer's disease may fail to recognize numbers.[15]

Making judgments and decisions

Alzheimer's disease complicates the ability to make rational decisions and judgments. Individuals may make unwise choices in social situations or dress inappropriately for the weather. Everyday challenges may become overwhelming. A person with Alzheimer's disease might struggle to address a burning meal on the stove or make decisions while

driving.[16]

Planning and performing familiar tasks

Routine activities that require following a sequence of steps can also pose difficulties for individuals with Alzheimer's disease. They may find it hard to plan and prepare a meal or engage in activities they once enjoyed.[17]

Genetics and Risk Factors

Early-onset familial AD, though rare, is associated with mutations in the APP, PSEN1, and PSEN2 genes, whereas the more common late-onset form has a strong correlation with the APOE ε4 allele.[18]

Modifiable risk factors include cardiovascular disease, diabetes, obesity, and low physical or cognitive activity, while protective factors include higher education, Estrogen use, and a Mediterranean-style diet.[19]

Symptomatic Therapies for Alzheimer's Disease (AD)

Historically, there has been no definitive cure for AD, making symptomatic treatment the primary strategy in routine clinical practice.

There are two classes of medications authorized for the treatment of AD: cholinesterase inhibitors and partial N-methyl D-aspartate (NMDA) antagonists.[20]

Cholinesterase Inhibitors

Cholinesterase inhibitors work by enhancing the levels of acetylcholine, a neurotransmitter essential for communication between nerve cells, as well as for learning, memory, and cognitive abilities. Within this class, three drugs have been approved by the FDA for the treatment of AD: donepezil, Rivastigmine, and Galantamine.[21]

Donepezil

- Preferred medication
- Indicated for AD with mild dementia
- Acts as a rapid and reversible inhibitor of acetylcholinesterase
- Administered once daily in the evening

Rivastigmine

- Indicated for mild cognitive impairment (MCI) and mild dementia
- Functions as a slow, reversible inhibitor of both acetylcholinesterase and butyrylcholinesterase
- Available in both oral and transdermal forms

Galantamine

- Approved for MCI and mild dementia
- Acts as a rapid, reversible inhibitor of acetylcholinesterase
- Available in a twice-daily tablet or a once-daily extended-release capsule
- Not suitable for individuals with end-stage renal disease or severe liver dysfunction

The most frequently observed side effects of cholinesterase inhibitors include gastrointestinal issues such as nausea, vomiting, and diarrhea. These medications may also lead to bradycardia, cardiac conduction abnormalities, and syncope due to increased vagal tone. They are contraindicated in patients with significant cardiac conduction issues.[22]

Partial N-Methyl D-Aspartate (NMDA) Antagonist Memantine

The partial NMDA antagonist memantine inhibits NMDA receptors, which helps to reduce intracellular calcium buildup. The FDA has approved it for the treatment of moderate to severe AD. Common side effects include dizziness, body aches, headaches, and constipation.[23]

Therapies for Treatment and Management in Alzheimer's Disease

Amyloid Related Imaging Abnormalities (ARIA)

ARIA refers to an immune-mediated reaction to therapies targeting amyloid within the cerebral vascular walls, leading to capillary leakage into perivascular spaces and hemorrhages in cortical and leptomeningeal arteries. There are two radiological forms of ARIA: ARIA edema (ARIA-E) and ARIA hemorrhage (ARIA-H).[24]

ARIA is recognized as a side effect linked to amyloid immunotherapies. The presence of the apolipoprotein E4 allele and findings of cerebral amyloid angiopathy on brain MRI are the most significant risk factors for the development of ARIA in patients undergoing treatment with amyloid immunotherapies.[25]

In the phase I/II trials of Aducanemab, ARIA-E and ARIA-H were observed in 26.1% to

26.7% and 26.1% to 30.5% of participants, respectively. Importantly, most of these individuals were asymptomatic.[26]

Other Management Strategies in AD

When managing Alzheimer's Disease (AD), it is crucial to address coexisting symptoms such as anxiety, depression, and psychosis, particularly in the mid to late stages of the illness.[27]

It is recommended to avoid tricyclic antidepressants due to their anticholinergic properties, which may exacerbate cognitive decline. Antipsychotic medications should be administered with caution for acute agitation, only after other interventions have been attempted and when the safety of the patient or caregiver is at stake.[28]

Typically, other medications are explored before considering antipsychotics, which usually include SSRI antidepressants like citalopram and anticholinesterase agents such as donepezil.

Second-generation antipsychotics are generally preferred over first-generation options due to their improved safety profile and reduced risk of extrapyramidal side effects. In May 2023, the FDA approved Brexpiprazole for the treatment of agitation associated with dementia due to AD.[29]

However, the limited benefits of these medications should be carefully weighed against the minor risks of stroke and increased mortality. The overarching principle in the use of antipsychotics is to administer the lowest effective dose to alleviate the patient's agitation.[30]

ADVANCED DIAGNOSIS FEATURE IN AD

Timely and precise diagnosis of Alzheimer's Disease (AD) is crucial for delivering suitable care, controlling symptoms, and formulating specific interventions. The diagnostic methods for AD include a blend of clinical evaluations, cognitive assessments, and sophisticated neuroimaging techniques (Assunção et al., 2022).[31] A systematic approach to the diagnosis and management of AD is illustrated in Fig. 3.

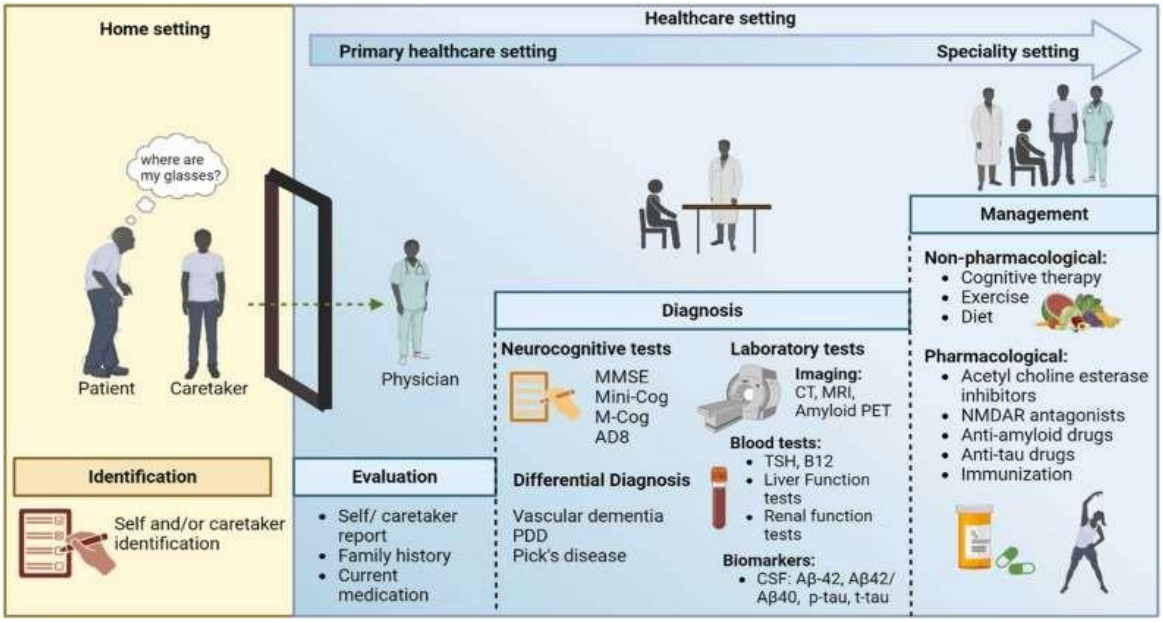
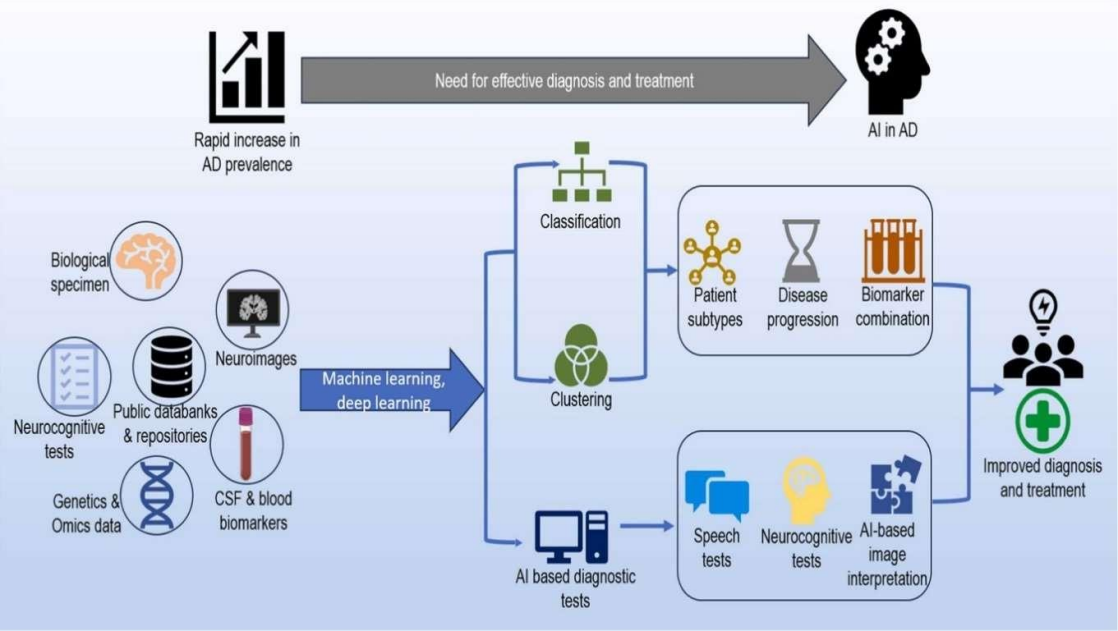


Fig. 3: A systematic approach to managing Alzheimer's Disease (AD). The management steps for AD can be categorized into Identification, Evaluation, Diagnosis, and Management. The various tests and tools utilized in each step are displayed in their corresponding columns. Initially, cognitive changes and memory issues are recognized by the patient or their caregiver at home.[32]

Within a healthcare environment, the physician assesses the patient, reviews their family history and medication status, and may refer them to a specialist. Neurocognitive assessments such as the MMSE, Mini-Cog, M-Cog, AD8, along with imaging techniques like MRI and Amyloid PET, as well as biomarkers such as Aβ42/Aβ40 and p-tau, along with various blood tests, are employed in the diagnosis of AD. Following diagnosis, both pharmacological and non-pharmacological treatments are implemented for managing AD.[33]

- Cognitive and neuropsychological assessments
- Neuroimaging methods
- Computed tomography (CT)
- Structural magnetic resonance imaging (sMRI)
- Cognitive and neuropsychological assessments
- Positron emission tomography (PET)
- Functional MRI (fMRI)
- Biomarkers
- Artificial intelligence approach.



Machine Learning (ML) has been used in medical imaging for decades, particularly in computer-aided diagnosis and functional brain imaging. Initially, ML helped doctors identify clear disease indicators.[34] As ML techniques advanced, they began addressing more complex medical detection issues. An unsupervised ML model, the Conditional Restricted Boltzmann Machine (CRBM), was applied to 18-month data from 1,909 patients with mild cognitive impairment (MCI) or Alzheimer's Disease (AD) to accurately model AD.[35]

A study identified key brain regions associated with AD. ML often requires manual feature extraction, complicating the analysis of large datasets.[36]

CONCLUSION

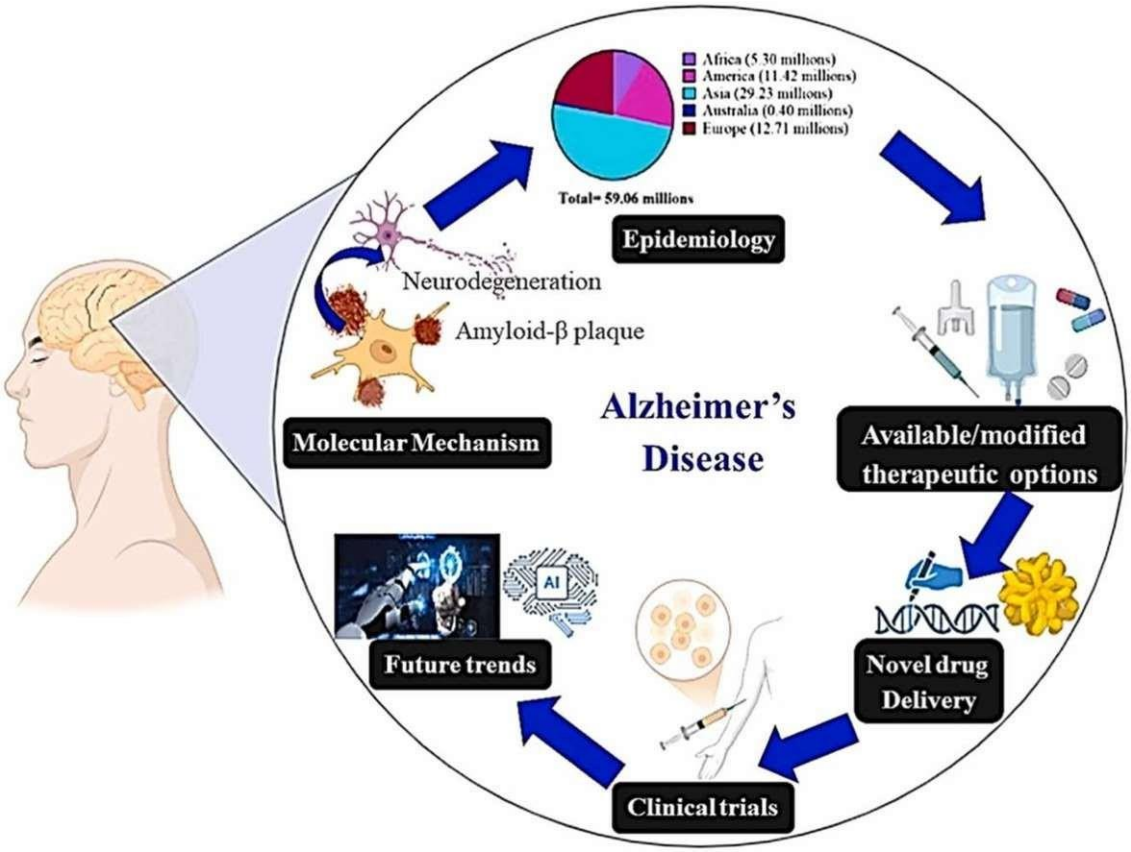
The conclusion examines the changes in caregiver and patient life-writing over thirty years, highlighting these shifts through a multilingual perspective. It attributes these changes to the rising number of dementia diagnoses and increased societal awareness of the disease.[37]

This evolution has fostered a patient-centered approach, with more patients actively participating in shaping the discourse on dementia and self-identity. Recent third-person caregiver narratives, including a graphic novel and a documentary, illustrate how this shift in patient perception is influencing broader societal values, healthcare planning, and cultural views on dementia.[38]

Clinical Implications and Future Directions

Management requires a multidisciplinary approach involving pharmacologic treatment, behavioral interventions, caregiver support, and advanced planning. With global prevalence projected to quadruple by 2050, the development of effective disease-modifying treatments and scalable diagnostic tools is urgent.[39]

Integration of biomarker-based diagnostics and precision medicine strategies(AI) may revolutionize early detection and individualized care in the coming decade.[40]



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