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"A Comprehensive Review on Alzheimer's Disease: Current Understanding and Future Prospects"

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ABSTRACT

Alzheimer's disease is a common type of dementia with distinctive brain abnormalities, including amyloid-beta plaque and tau tangle formations. Biochemical abnormalities, including disruptions in protein metabolism, oxidative stress, inflammation, and neurotransmitter pathways, are found in the complex pathophysiology. Notably, compromised glucose uptake by the brain, concomitant with the presence of neurotoxic Aβ42, precipitates a cascade of pathological events, inducing detrimental reactive oxygen species (formation. The pervasive nature of Alzheimer's disease, as the predominant cause of dementia, is underscored by its escalating global prevalence, anticipated to burgeon to an alarming 136 million by 2050. Despite its profound societal impact, extant therapeutic modalities remain palliative, accentuating the urgency for transformative interventions. This exhaustive review intricately navigates the diagnostic odyssey, wherein meticulous clinical assessments, neurological evaluations, and advanced imaging converge for precision. A pivotal juncture in this diagnostic trajectory involves adherence to the NINCDS-ADRDA criteria, providing a standardized rubric incorporating clinical, cognitive, and biomarker evidence. This scientific exposition culminates in a tableau delineating the current pharmacotherapeutic landscape, featuring drugs like aducanumab, lecanemab, and BACE inhibitors, poised at different phases of clinical scrutiny. The narrative then pivots toward futuristic trajectories, contemplating precision medicine paradigms, innovative biomarker-driven diagnostic modalities, and the exploration of synergistic therapeutic approaches. Embarking on an intellectual journey through the annals of Alzheimer's disease research and treatment, this comprehensive review explores the intricate molecular tapestry of the condition whilst envisioning a promising future era of tailored and efficacious interventions.

Keywords: Alzheimer's disease (AD), Dementia, Amyloid plaque, ApoE, tau.

I. INTRODUCTION:

Alzheimer's disease (AD), the most common type of dementia, is named after the well-known German psychiatrist Alois Alzheimer. It is distinguished by unique abnormalities in the brain, such as the production of plaques and tangles of amyloid-beta peptide (Aβ). These aberrations are most typically found in the neocortical areas and the medial temporal lobe.[1]Emil Kraepelin discovered AD after observing these plaques and severe neuron loss in a memory-impaired patient.[2]

AD is a complex disease with a rich pathophysiologyinvolving various metabolic alterations. Problems with amyloid precursor protein metabolism, tau protein phosphorylation, oxidative stress, reduced energy generation, dysfunctional mitochondria, inflammation, membrane lipid abnormalities, and disruptions in neurotransmitter pathways are among these changes.[3]It is worth mentioning that many clinical features are related to metabolic abnormalities, emphasizing the critical role of metabolic dysfunction in the genesis and progression of Alzheimer's disease. One recurring hallmark of the disease is decreased glucose uptake by the brain, which begins long before cognitive impairment becomes clear. Aβ42, a neurotoxic chemical, contributes to decreased energy generation in neurons by inducing a sequence of pathogenic processes. The interaction of Aβ42 with mitochondrial enzymes results in the generation of potentially dangerous reactive oxygen species (ROS). These ROS have a harmful impact on important physiological processes such as

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glycolysis, the tricarboxylic acid (TCA) cycle, and mitochondrial respiratory chain activity.[4]

AD, the most common cause of dementia, primarily destroys episodic memory and finally culminates in cognitive function impairment.[1]In 2013, it was estimated that over 44 million people worldwide were affected by dementia; however, this figure is expected to skyrocket to almost 136 million by the year 2050.[5]Despite the disease's widespread prevalence, there are currently no therapies in place to slow its progression. Progressive cognitive decline can be caused by brain disorders such as AD or other factors such as drunkenness, infections, lung and circulatory system abnormalities, nutritional inadequacies, vitamin B12 insufficiency, tumours, and more. So far, an estimated 50 million people worldwide have been diagnosed with AD.[6]This figure is expected to double every five years, totalling 152 million instances by 2050.[5]The economic costs of this terrible disease are projected to be $1 trillion each year, putting a tremendous strain on worldwide economies.While a cure for AD remains elusive, current treatments focus mainly on symptom relief. This comprehensive review seeks to provide a concise analysis of AD diagnosis, underlying pathology, suspected causes, and latest treatment possibilities.[7]It will also highlight the most recent advances in developing compounds that target critical disease-related mechanisms, such as the aggregation and misfolding of A and tau proteins, inflammation, oxidative damage, and other critical factors, as well as potential therapeutic interventions aimed at changing lifestyle and improving cognitive abilities.[8]These breakthroughs hold the potential to transform the future by offering powerful interventions that can change the trajectory of this prevalent and destructive illness.

ETIOLOGY:[2,9-11]

The Aetiology of AD is complex and not fully understood. However, several factors have been identified as potential contributors to the development of the disease.

- **Genetic Factors:** Certain genetic mutations, such as those in the APP, PSEN1, and PSEN2 genes, can increase the risk of developing AD.
- **Age:** Advancing age is the most significant risk factor for AD. The likelihood of developing the disease increases with age.
- **Family History:** Having a family history of AD can increase an individual's risk of developing the condition.
- **Lifestyle factors:**Smoking, obesity, and lack of physical activity are lifestyle factors associated with an increased risk of AD. Unhealthy dietary patterns and limited cognitive stimulation also contribute to the risk.
- **Apolipoprotein E (APOE) gene:** Variants of the APOE gene, particularly the APOE ε4 allele, are associated with an increased risk of developing late-onset AD.
- **Vascular Factors:** Conditions that affect blood vessels, such as high blood pressure, high cholesterol, and diabetes, may contribute to the development of AD.
- **Inflammation:** Chronic inflammation in the brain may play a role in the progression of AD.
- **Oxidative Stress:**An imbalance between the production of reactive oxygen species and the body's ability to neutralize them can lead to oxidative stress, which may contribute to AD.
- **Environmental Factors:** Exposure to certain environmental factors, such as air pollution, heavy metals, and pesticides, has been suggested as a potential risk factor for AD.

EPIDEMIOLOGY:

AD is the major cause of dementia, accounting for 60-80% of all cases. It affects millions of people worldwide. Its incidence becomes more prevalent as individuals reach older age, notably among those who are 65 years or older.[12] This global health concern, highlighted by the World Health Organization (WHO), saw approximately 50 million individuals living with dementia in 2020, with AD being the primary cause. The risk of AD rises significantly with age, doubling every five years after 65, though early-onset cases, while rare, can occur in those under 65.[10,11] Notably, women show a higher prevalence, partially attributed to their longer life expectancy. Beyond the individuals diagnosed, AD places a substantial burden on caregivers, often family and friends, leading to physical, emotional, and financial challenges.[11,12,14] Economically, AD exerts a significant toll, encompassing healthcare, long-term care, and productivity costs, a burden expected to surge with an aging population.[13,14] Regional disparities in prevalence reflect the influence of genetics, lifestyle, education, and healthcare access by 2023, the incidence of AD worldwide is projected to reach a staggering 50.7

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million, as predicted by the AD & Related Disorders Society of India (ARDSI).[15]The number of cases is expected to soar in the coming years by 2030, the global population is expected to soar to an impressive 75.6 million, reaching a staggering 131.5 million by 2050. In India alone, experts predict a steady increase in cases, with approximately 4.21 million projected for 2023. Experts are predicting an astonishing increase in numbers, with a staggering rise to 5.76 million by 2030, and an even more impressive 14.3 million by 2050.[5,6] The growth rate of the global population is astonishing, currently standing at 0.84%. Yet, India takes the lead with an even higher growth rate of 0.93%. The number of individuals affected by AD worldwide is projected to increase significantly by 2023, reaching a staggering total of 51.3 million cases. India is specifically projected to contribute significantly to this figure, with an estimated 4.27 million cases.[15]

PATHOPHYSIOLOGY:

The pathophysiology of AD involves a complex interplay of various factors that contribute to the development and progression of the disease.

- **Amyloid-beta (Aβ) Plaques:** The accumulation of Aβ plaques in the brain is a hallmark of AD. Aβ peptides are derived from the breakdown of Amyloid precursor protein (APP). In AD, there is an imbalance between the production and clearance of Aβ, leading to the formation of plaques. [1,2]

- **Neurofibrillary Tangles:** Another characteristic feature of AD is the presence of neurofibrillary tangles. These tangles are formed by the abnormal aggregation of tau protein, which handles maintaining the structure and stability of neuronal cells. In AD, tau protein becomes hyperphosphorylated and forms tangles, disrupting the normal functioning of neurons.[1,9,12]

- **Neuronal Loss and Atrophy:** Over time, the accumulation of Aβ plaques and neurofibrillary tangles leads to the degeneration and loss of neurons, particularly in brain regions involved in memory and cognitive function. This neuronal loss results in brain atrophy, which is commonly observed in individuals with AD.[12,16]

- **Neurotransmitter Imbalance:**AD is associated with disruptions in neurotransmitter systems, particularly acetylcholine. The degeneration of cholinergic neurons, which produce acetylcholine, contributes to cognitive impairments seen in the disease.[12,16,17]

- **Inflammation:** Chronic inflammation is a prominent feature of AD. Activated immune cells, such as microglia, release inflammatory molecules that contribute to neuronal damage and further progression of the disease.[17]

- **Oxidative Stress:** Increased production of reactive oxygen species (ROS) and decreased antioxidant defences lead to oxidative stress in AD. Oxidative stress can damage cellular components and contribute to neuronal dysfunction and death.[18]

- **Mitochondrial Dysfunction:** Mitochondria, the energy-producing organelles in cells, play a crucial role in neuronal function. In AD, mitochondrial dysfunction occurs, leading to impaired energy production and increased production of ROS.[19]

- **Disrupted Synaptic Function:** Synapses, the connections between neurons, are essential for communication and information processing in the brain. AD disrupts synaptic function, impairing neuronal communication and contributing to cognitive decline.[17-19]

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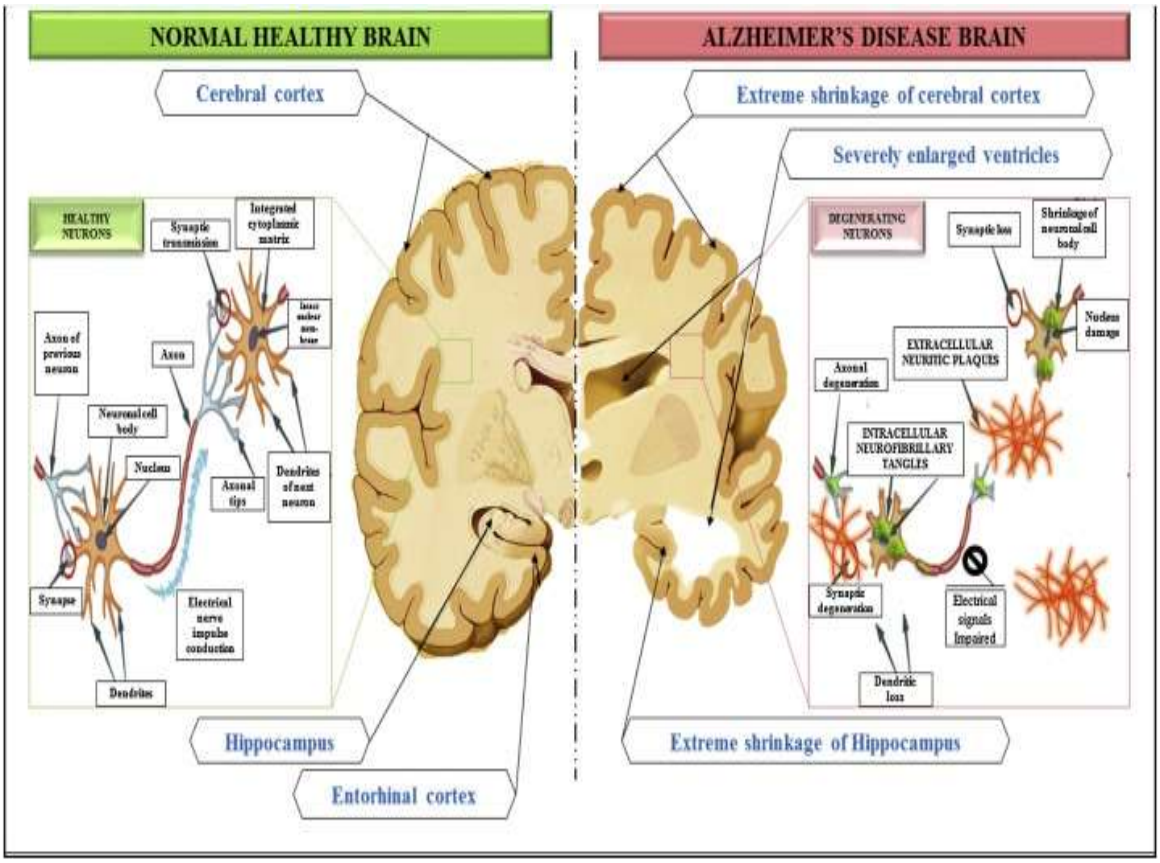

Fig 1: Schematic diagram comparing a normal healthy brain and a brain at a severe stage of Alzheimer's disease.[20]

SIGNS AND SYMPTOMS:

AD is a progressive neurodegenerative disorder that primarily affects cognitive function and memory. While the symptoms can vary among individuals, there are some common early signs and neuropsychiatric manifestations associated with the disease.

a) Early Signs:

- **Memory Loss:**An initial sign of AD that stands out is the challenge of memorizing fresh information. This can manifest as forgetting recently learned information, events, or conversations. Individuals may also rely heavily on memory aids such as reminder notes or electronic devices. Additionally, they may ask the same questions repeatedly, seeking reassurance or clarification.[21,22]
- **Difficulty in Completing Everyday Tasks:**AD can make it challenging for individuals to perform routine tasks that were once familiar and effortless. This can include activities like organizing a grocery list, following a recipe, or playing their favourite games. They might encounter difficulties in devising plans, finding solutions, and effectively carrying out tasks involving numerous steps.[23-24]
- **Confusion with Time and Place:** People with AD often experience confusion regarding their current location or how they arrived there. They may forget important dates, seasons, or even the passage of time. This can lead to disorientation and a sense of being lost, even in familiar surroundings.[21,22]
- **Misplacing and Losing Items:** Another common symptom is misplacing objects and subsequently being unable to retrace their steps to find them. For example, an individual may put their keys in a specific spot but later forget where they placed them. This can cause frustration and anxiety.[22,25]
- **Poor Judgment:** AD can affect an individual's judgment and decision-making abilities. They may exhibit changes in their ability to manage finances, make sound decisions, or maintain

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personal hygiene. These changes can be subtle at first but become more noticeable as the disease progresses.[23,25]

b) Neuropsychiatric Manifestations:

- **Psychotic Symptoms:**People diagnosed with AD may suffer from troubling symptoms related to psychosis, including delusions and hallucinations. Delusions are strong irrational beliefs that persist despite contradictory evidence on the contrary, hallucinations consist of perceiving non-existent entities In Alzheimer's, hallucinations tend to be visual but can sometimes be auditory. The hallucinations and delusions seen in AD are distinct from those found in other mental health disorders like schizophrenia, psychosis, depression, or mania. It is important to acknowledge this crucial distinction.[26-28]
- **Agitation:** Agitation refers to excessive motor activity, restlessness, or verbal and physical aggression accompanied by emotional distress. It is a common symptom in AD and is associated with structural and functional abnormalities in brain regions responsible for emotional regulation. Agitation and aggression have been linked to changes in certain neurotransmitters, such as acetylcholine and serotonin, as well as the accumulation of tau protein.[25,28]
- **Apathy:**Apathy, a striking symptom associated with Alzheimer's disease, is characterized by a profound absence of motivation, emotional indifference, and a noticeable decline in voluntary muscle movements. Apathy worsens with disease, starting with normal cognition, progressing to mild impairment, and ending in dementia. Studies show apathy is linked to impaired cortical function in certain brain regions, including the posterior cingulate and inferior temporal cortex, with atrophy and reduced metabolism. Apathy in AD may be linked to neurotransmitter changes (such as GABA and dopamine) and increased levels of tau and phosphate in cerebrospinal fluid.[28-30]
- **Depression:** Depression is common in individuals with AD, with studies reporting rates of around 16% in population-based samples and 44.3% in clinical settings. Depression can also occur in individuals with mild cognitive impairment (MCI), which is often a precursor to AD. Alongside apathy, depression is considered an indicator of disease progression from normal cognition to MCI and eventually to dementia. Changes in brain pathology, including the presence of tau, amyloid, and vascular disease, have been observed in individuals with AD and comorbid depression. These changes are often associated with a significant loss of serotonin and serotonin transporter binding, which may have implications for treatment.[14,15,29,30]

DIAGNOSIS

The diagnostic process for AD is an intricate and comprehensive journey that incorporates various methodologies to ensure precision. Here's a detailed breakdown of the expansive diagnostic process:

Clinical Assessment:

The diagnosis of AD is a meticulous and comprehensive process that adopts a holistic approach to ensure precision. Commencing with a thorough exploration of the patient's medical history, which considers pre-existing conditions, medications, and cognitive changes over time, the initial phase lays the foundation for a comprehensive evaluation.[31]Behavioural observations, often supplied by family members, relatives, and neighbours, play a pivotal role in deciphering memory-related challenges and behavioural patterns.In this diagnostic journey, medical professionals, especially neurologists, collaborate closely with physicians to conduct neurological and neuropsychological assessments, offering a comprehensive evaluation of cognitive function.[17,32,33] Advanced imaging techniques, including CT scans, MRI, SPECT, and PET, contribute significantly by eliminating cerebral pathology and aiding in predicting the progression from mild cognitive impairment to AD.[34]

A cornerstone in AD diagnosis is the utilization of established criteria such as the NINCDS-ADRDA criteria. The criteria for the diagnosis of AD were initially established by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the AD and Related Disorders Association (ADRDA) in 1984.[35] These criteria were further revised and improved in 2007. They provide a standardized benchmark, incorporating clinical, cognitive, and, when feasible, biomarker evidence for a more accurate diagnosis. Continual advancements in medical science introduce histopathological confirmation into the diagnostic landscape, involving a meticulous microscopic examination of brain tissue.[36,37] This additional

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step further solidifies the accuracy of the diagnosis. In the early stages, accurate neurological assessments are essential in differentiating AD from other conditions. Family members and caregivers are important in Alzheimer's diagnosis and management. Their insights are invaluable for understanding the patient's condition, behaviours, and daily living abilities.[38,39] This collaborative and comprehensive approach ensures a nuanced understanding of the patient's condition and facilitates the implementation of effective management strategies.

TREATMENT APPROACHES FOR ALZHEIMER'S DISEASE:

AD lacks a definitive preventive measure, with conflicting outcomes from global studies on potential preventive measures. Epidemiological studies suggest links between modifiable factors like diet and cardiovascular risk, but clinical trials are essential to validate their preventive efficacy.

- **Non-Pharmacological Treatment:**

Non-pharmacological approaches aim to maintain or enhance cognitive capacities and quality of life. Strategies include art therapy, activity-based therapy, and memory training. While these don't alter Alzheimer's course, systematic reviews indicate positive outcomes from activities like exercise and cognitive engagement.[40-42]

- **Pharmacological Treatment:**

Five FDA-approved medications treat AD symptoms, including Donepezil, Galantamine, Rivastigmine (cholinesterase inhibitors), and Memantine (NMDA receptor antagonist). These drugs aim to preserve acetylcholine levels and regulate neurotransmitters. Advances in research focus on inhibiting β and γ secretase pathways for neuroprotection. Cholinesterase Inhibitors like Donepezil, Galantamine, and Rivastigmine are commonly prescribed cholinesterase inhibitors. They inhibit acetylcholinesterase, preventing acetylcholine breakdown. The first-generation inhibitor, Tacrine, is no longer used due to tolerability issues.[39,40]

- **Role of Medicinal Plants:**

Medicinal plants and compounds, including Curcuma longa, Bacopa monnieri, Ginkgo biloba, and Zingiber officinale, prove promising neuroprotective benefits attributed to their anti-inflammatory, anti-amyloidogenic, and antioxidant properties.[41] Additionally, compounds such as resveratrol, berberine, luteolin, and rosmarinic acid hold potential in the prevention and reduction of Alzheimer's symptoms.[42] The list of medicinal plants encompasses Curcuma longa (Turmeric), Bacopa monnieri (Brahmi), Convolvulus pluricaulis (Shankhpushpi), Centella asiatica (Gotu Kola), Ginkgo biloba (Maidenhair Tree), Zingiber officinale (Ginger), along with others like quercetin, resveratrol, berberine, luteolin, and rosmarinic acid, all contributing to neuroprotection.[43]

CURRENT ADVANCEMENTS IN ALZHEIMER'S DISEASE TREATMENT

Monoclonal antibodies, such as aducanumab and lecanemab, have gained FDA approval, targeting amyloid plaques, a hallmark of AD.[44]Beta-secretase (BACE) inhibitors, aimed at reducing amyloid beta production, and tau-targeted therapies are under investigation, showcasing a multifaceted approach to tackling AD pathology.[45] Non-drug therapies, including cognitive training programs and lifestyle interventions like diet and exercise, have been explored to maintain cognitive abilities and reduce the risk of AD. Research has also extended to supportive services and caregiver interventions, recognizing the importance of holistic care.[46] Ongoing clinical trials encompass diverse drug candidates addressing different facets of AD. The exploration of gene therapy and precision medicine reflects a growing understanding of the genetic components of AD. Advances in imaging techniques contribute to early and accurate AD diagnosis.

Drug	Type	Mechanism of action	Phase	Reference
Aducanumab	Monoclonal antibody	Targets amyloid plaques	FDA-approved	[47]
Lecanemab	Monoclonal antibody	Targets amyloid plaques	FDA-approved	[48]
Donanemab	Monoclonal antibody	Targets amyloid plaques	Phase 3	[49]
BACE inhibitors	Blocks the production of amyloid beta	Reduce amyloid plaque formation	Phase 2/3	[50]
Tau inhibitors	Block the aggregation of tau protein	Prevent tau tangles from forming	Phase 2/3	[51]

Table 1: Current Status of Drug Therapies in Alzheimer's Disease.

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II. FUTURE DIRECTIONS

The field of AD(AD) research and treatment is seeing the emergence of several exciting future directions One key avenue involves precision medicine approaches, tailoring treatments based on individual genetic, molecular, and lifestyle factors to optimize effectiveness. Our attention is also directed towards early detection and diagnosis, as we strive to identify biomarkers and develop innovative imaging techniques that can detect AD in its earliest stages Another promising area involves exploring combination therapies andinvestigating the benefits of simultaneously targeting multiple aspects of the disease. Immunotherapies, including vaccines and antibody treatments, are under extensive scrutiny for their potential to enhance the body's ability to combat AD-related abnormalities. Non-drug methods like cognitive training, exercise, and dietary approaches are being improved for better symptom management and prevention Targeting neuroinflammation is an essential area of investigation, to comprehend and effectively address its impact on the progression of AD. Encouraging global collaborations, involving individuals with AD and caregivers in the research process, leveraging technological innovations like artificial intelligence, and advocating for streamlined regulatory processes are additional future directions. These collective efforts hold immense potential to revolutionize our comprehension of AD, paving the way for treatments that are not just superior in efficacy, but also individually tailored and effortlessly accessible to all.

III. CONCLUSION

Alzheimer's disease, a prevalent form of dementia, is influenced by both genetic and environmental factors that contribute to distinctive neuropathological characteristics. Characterized by the presence of amyloid plaques, tau protein abnormalities, and a cascade of events that ultimately result in neurodegeneration. Diagnosis involves clinical assessments and imaging with input from caregivers. Various treatments are available, including both medication and non-pharmacological methods. Future advancements aim to improve precision medicine, early detection, and new therapies.

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