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A Review on Alzheimer's Disease

Munshi Shaikh Rahat
munshishaikhrahat@gmail.com
Godavari Institute of Pharmacy, Kolpa, Maharashtra

Maniyar Hassan
hassanmaniyar300@gmail.com
Godavari Institute of Pharmacy, Kolpa, Maharashtra

Surwase Mohini
mohinisurwase2003@gmail.com
Godavari Institute of Pharmacy, Kolpa, Maharashtra

Bagwan Wasim
bwasim111@gmail.com
Godavari Institute of Pharmacy, Kolpa, Maharashtra

Kasture Pranav
pranavkasture2004@gmail.com
Godavari Institute of Pharmacy, Kolpa, Maharashtra

Sustarphod Vijay
vsustarphod@gmail.com
Godavari Institute of Pharmacy, Kolpa, Maharashtra

Budge Ganesh
ganeshbudge85@gmail.com
Godavari Institute of Pharmacy, Kolpa, Maharashtra

Chandel Adityasingh
adtiyasinghchandel2003@gmail.com
Godavari Institute of Pharmacy, Kolpa, Maharashtra

ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by a gradual decline in cognitive function, which affects memory, thinking, and reasoning abilities. As the disease advances, individuals experience worsening impairments in daily activities and exhibit behavioral changes. This condition is the most common cause of dementia, with a significant impact on quality of life for both patients and caregivers. Alzheimer's disease (AD) is the most common form of both pre-senile and senile dementia, affecting about 5% of men and 6% of women over the age of 60 worldwide, according to the World Health Organization (WHO). The disease typically begins with subtle memory failure, which progressively worsens and can become debilitating. Current treatments offer minimal impact, including acetylcholinesterase inhibitors (rivastigmine, galantamine, donepezil) and the NMDA receptor antagonist memantine. While these drugs can slow disease progression and relieve symptoms, they do not cure or prevent the disease's onset. Although the neuropathological features of AD are known, the exact mechanisms behind the disease remain unclear, which contributes to the lack of effective treatments. However, recent advances in understanding AD's pathophysiology have led to new therapeutic targets that may directly address the underlying disease process. This article discusses these recent developments in AD research and how they could potentially improve disease management and reduce care costs. It highlights the importance of advancing knowledge in this area for better treatment outcomes.

Keywords: *lzheimer's, Management, Diagnosis, Treatment, Therapy, Types & Phases of Dementia.*

INTRODUCTION:

Alzheimer's disease (AD) is the most common cause of dementia. The disease is marked by a gradual decline in cognitive function, beginning with episodic memory problems. Globally, dementia affected approximately 44 million people in 2013, with a predicted increase to 136 million by 2050. Despite the high prevalence [1], no treatments have been proven to modify the course of the disease, making it a significant unmet medical need in neurology.

AD pathology involves multiple biochemical changes, including abnormalities in amyloid [2] precursor protein metabolism, tau protein phosphorylation, oxidative stress, mitochondrial dysfunction, inflammation, and disrupted neurotransmitter pathways. These features are closely linked to 'metabolic dysfunction'. One of the earliest signs of AD is impaired cerebral glucose uptake, which occurs long before cognitive symptoms appear. A key factor in AD neurotoxicity is the protein 'Aβ42', which interacts with mitochondrial enzymes and contributes to mitochondrial damage, leading to increased release of reactive oxygen species (ROS). These ROS further disrupt metabolic processes like glycolysis, the tricarboxylic acid (TCA) cycle, and mitochondrial respiratory chain activity.[1,37]

NORMAL MEMORY

The process of ageing emphasizing that understanding these processes is crucial for
comprehending the complexities of 'dementia'. The distinction between normal ageing and abnormal conditions like dementia is highlighted. In normal ageing, there are biological, social, and psychological components, and these aspects often interact with each other.

For example, a physical change like 'arthritis' can affect mobility, which in turn may lead to reduced social interaction or

psychological impacts, all of which can influence cognitive health.

Defining “normal ageing” and distinguishing it from ‘abnormal conditions’ like dementia.
It highlights that ‘normality’ is not a fixed or absolute concept but rather a ‘range of variations’, and this range can differ widely between cultures, environments, and individuals.
The boundariesbetween what is considered "normal" and "abnormal" are often
blurry, especially when comparing cognitive and physical changes across the lifespan. The paper also addresses how changes in one area of ageing (such as physical health) can impact others (such as social interaction or cognitive function). For example, physical conditions like arthritis might limit mobility, which in turn affects social engagement and mental health. These interconnected factors are critical when comparing an individual’s past and present cognitive abilities

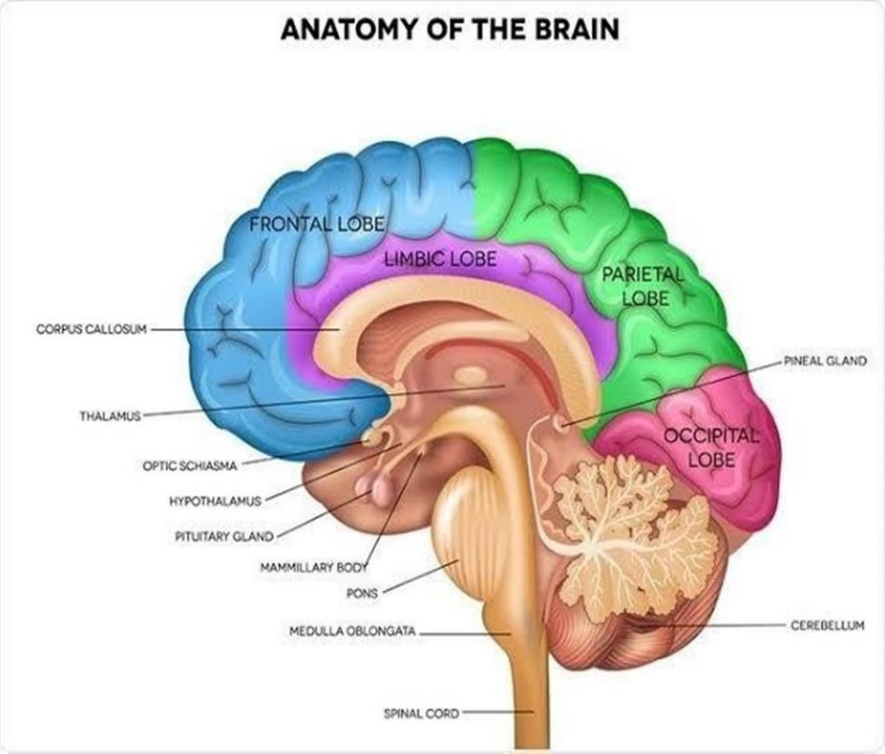

Fig 1: Anatomy of brain:

TYPES OF MEMORY

1. Semantic and episodic memory:

Episodic memory:
Refers to the ability to recall specific events or experiences, such as remembering what you had for breakfast. These memories are tied to particular moments in time.

Semantic memory:
On the other hand, refers to factual knowledge that is not tied to specific events or experiences. For example, knowing that the word "breakfast" refers to the morning meal is semantic memory.

Declarative and procedural memory:

Declarative memory:
includes both semantic and episodic memories, which involve
Knowledge that can be consciously recalled, including facts (semantic memory) and personal experiences (episodic memory).

Procedural memory:
involves the memory for skills, habits, and routines that we perform
Without tconscious thought, such as knowing how to drive a car or ride a bike.
Older adults can still learn as much as younger individuals, but they generally require more time to achieve the same level of learning because they process and absorb information more slowly. This slower processing speed is a typical age-related change and can be exacerbated by factors like depression. However, when noticeable memory decline occurs
and persists, it could signal the onset of dementia, especially if accompanied by other cognitive dysfunctions.[11]
Memory Failure and Dementia:
There are four types:
1. Registration –
The initial process of paying attention and perceiving information.

2. Encoding –
The process of transforming information into a form that can be stored in memory, which Can be done semantically (in terms of meaning) or phonologically (in terms of sound).
3. Storage –
The maintenance of information in memory.

4. Retrieval –
The process of accessing stored information when needed.
memory to function For properly, all four stages must work smoothly. In cases of dementia ,there are disruptions in these stages, which contribute to the difficulty in recalling information.

DEMENTIA

It is a syndrome characterized by disturbances in several brain functions, not just memory, but also thinking, orientation, comprehension, language, and learning capacity. These disturbances typically worsen over time, making early detection and assessment of memory problems
crucial in diagnosing dementias. This section provides an overview of 'dementia' as a syndrome, its stages, and how it impacts individuals differently. Key points include:

Cognitive and Emotional Effects of Dementia:
'Cognitive impairments' in dementia often manifest as 'memory loss', but may also affect other cognitive functions such as thinking, orientation, and judgment. Importantly, 'consciousness remains clear' meaning individuals with dementia are generally aware of their surroundings, even as their cognitive abilities decline.[32]

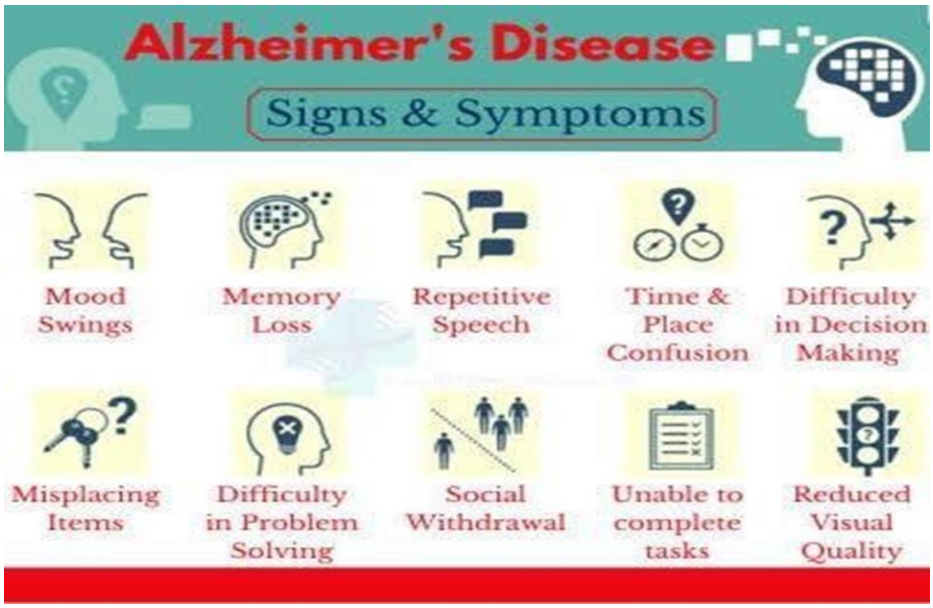

Fig 2 : Sign and symptoms:

Three stages of dementia:
1. Early Stage:
The first 1-2 years. Symptoms may include mild memory loss, difficulty with familiar tasks, and subtle changes in behavior or judgment.
Generally the fifth year and beyond. Cognitive decline is severe, and individuals may lose the ability to communicate, require assistance with daily activities, and experience significant changes in physical health. Variability in Dementia Symptoms.[12]

2. Middle Stage:
Typically the second to the fourth or fifth years, Symptoms become more noticeable and
disabling, including more pronounced memory problems, confusion, difficulty with communication, and greater changes in personality or mood.
3. Late Stage:
Generally the fifth year and beyond. Cognitive decline is severe, and individuals may lose the ability to communicate, require assistance with daily activities, and experience significant changes in physical health. Variability in Dementia Symptoms.[12]

These stages are rough 'guidelines', and not all individuals with dementia will
experience the same 'timing' or 'symptoms'. Some may progress more slowly or exhibit symptoms earlier than others.

GENETIC AND RISK FACTORS IN ALZHEIMER'S DISEASE

1. Genetics of Alzheimer's Disease:

Early-Onset AD:

This form of AD, which develops before the age of 65, is linked to rare genetic mutations.
One key gene involved is the Amyloid [2] Precursor Protein (APP) gene located on
chromosome 21. People with 'Down's syndrome' (trisomy 21), who have an extra copy of chromosome 21, have an increased risk of developing early-onset AD due to the presence of the APP gene.

Sporadic AD:

The genetics of sporadic (late-onset) Alzheimer's disease are more complex and less well understood. However, a significant risk factor is the presence of the epsilon-4 allele of the apolipoprotein E (APOE) gene, located on chromosome 19.[1,14]

2. Additional Risk Factors:

Gender:

Women have a higher prevalence [1] of AD compared to men, largely due to the fact that women tend to live longer, and 'age' is the primary risk factor for AD. [37]

Educational Attainment:

Lower levels of education are associated with an increased risk of AD. The theory is that higher education increases cognitive reserve, which helps the brain compensate for AD pathology.[42]

Cerebrovascular Risk Factors:

Conditions such as 'diabetes', 'hypertension', 'obesity', and 'smoking' significantly elevate the risk of developing AD. These factors contribute to 'vascular damage' and inflammation, which may exacerbate the development of dementia

Family History and Head Injury:

A family history of AD, particularly among 'first-degree relatives', and a history of 'head injury with loss of consciousness' are also known risk factors.

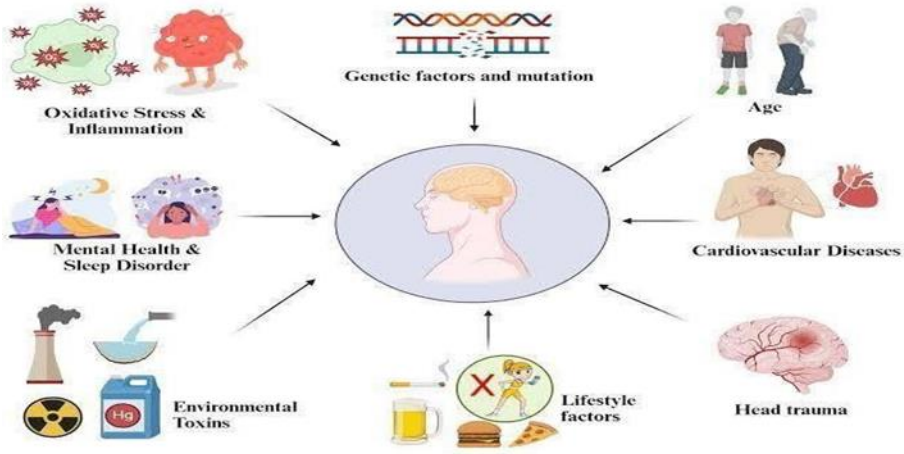

Fig 3: Genetic factors:

Establishing the Diagnosis [10] of Alzheimer Disease:

Establishing the diagnosis [10] of Alzheimer disease relies on clinical-neuropathology [8] assessment. Neuropathology [8] findings on autopsy examination remain the gold standard for diagnosis [10] of AD.

Cerebrospinal fluid (CSF). Decreased Aβ amyloid [2] 42 and increased tau-

The clinical diagnosis [10] of Alzheimer's disease, prior to confirmation by autopsy, is accurate approximately 80% to 90% of the time

Clinical signs. Slowly progressive dementia

Neuroimaging

Gross cerebral cortical atrophy on CT or MRI

Diffuse cerebral hypometabolism on PET

Neuropathologic findings. Microscopic β-amyloid [2] neuritic plaques, intraneuronal neurofibrillary tangles (containing tau

protein), and amyloid [2] angiopathy at postmortem examination. The plaques should stain positively with β-amyloid [2] antibodies and negatively with prion antibodies, helping to distinguish Alzheimer's disease from prion diseases. To support a diagnosis [10], the number of plaques and tangles must exceed those typically found in age-matched individuals without dementia, and established guidelines exist for their quantitative assessment. Additionally, aggregation of alpha-synuclein in the form of Lewy bodies may also be observed in neurons within the amygdala.[1]

NEUROPATHOLOGY AND CLINICAL SIGNS OF ALZHEIMER'S DISEASE (AD)

1. Clinical Diagnosis:
The accuracy of clinical diagnosis [10] for Alzheimer's disease is between 75% and 90%, with the highest accuracy among neurologists specializing in memory disorders and the lowest among general practitioners, who tend to over diagnose A. The diagnosis [10] can be challenging, especially in older patients who often have mixed types of dementia. There are no definitive laboratory tests or imaging techniques to confirm AD microscopic examination of brain tissue remains the only certain method for diagnosis [10]. Onset typically occurs from the age of 40, with a slow degeneration leading to death around 60 years post-onset.[15] Age-related brain atrophy and normal variability in brain size make diagnosis through gross brain examination difficult.[1]

2. Neuropathological Features:

AD brains typically show atrophy, particularly in the ‘medial temporal lobe’, with relatively spared ‘primary sensory and motor cortices’. The ‘hippocampus’ and ‘amygdal’ are often atrophic, and
the ‘lateral ventricles’ tend to be dilated .Neuronal and synaptic loss occurs, accompanied by the formation of ‘neurofibrillary tangles’ made of abnormal ‘tau [2] protein (paired helical filaments).

PHASES OF ALZHEIMER DISEASE

Each person with Alzheimer's disease will vary slightly in presentation according to personality. Emotional, behavioral and cognitive changes will also vary, but generally accepted by clinicians and researchers are stage model which describes broad characteristics.

In the **first phase**, the 'forgetfulness phase', there is usually difficulty in recalling recent events, and a tendency to forget where objects have been placed. Names of people and places, previously familiar, may be poorly recalled and a general disorientation persists and poor short- term memory.
The second recognized phase is the 'confusional phase'. Increasingly poor attention span and a decline in generalized intellectual performance are seen with a deteriorating memory. Disorientation in place, word-finding difficulty and other changes to speech may be seen.

Complex tasks are performed with difficulty, sometimes in a clumsy or inaccurate manner and often the skills the person learned last will be lost first. Lack of interest in news and
surroundings follows relatively quickly and can be extremely distressing to family and friends.

The third phase, the 'dementia phase', is characterized by a lack of purpose in the person's behavior which appears disjointed and sometimes bizarre Remaining intellectual and self-care abilities require constant supervision, as individuals in this phase experience further deterioration in memory capacity, calculating ability (dyscalculia), and various aspects of language, which become severely affected and eventually lost. Constant assistance is required for self-care skills such as grooming, dressing, and toileting and for feeding. A progressive physical wasting can also be seen which will mean help with walking. Sometimes one or two years of life will follow in an almost vegetative state until death. Environmental factors may have a role in triggering Alzheimer's disease in susceptible individuals. An association between Alzheimer's disease and aluminium has been formulated for several years.

PHARMACOLOGICAL THERAPY FOR ALZHEIMER'S DISEASE (AD):

The current treatment options and ongoing developments:

1. Current Pharmacological Treatments:
The available pharmacological therapies for Alzheimer's disease provide only ‘short-term symptom relief’ (typically 6 to 18 months). These treatments do not alter the underlying pathology of AD but help mitigate some of the cognitive symptoms.
The ‘two primary classes of drugs’ approved for symptom management are:

‘Cholinesterase inhibitors’ (e.g., Donepezil, Rivastigmine, Galantamine): These drugs increase the levels of ‘acetylcholine’, a neurotransmitter involved in memory and learning, by inhibiting the enzyme that breaks it down. This helps to compensate for the neuronal loss in the brain.

Memantine:
A ‘NMDA receptor antagonist’ that regulates glutamate activity in the brain, preventing excessive excitatory neurotransmission, which can be toxic and contribute to neuronal damage.
Limitations:

These drugs provide symptomatic relief but do not affect the disease's progression or pathology, meaning their benefits are temporary.

2. Future Directions:

The 'new medicines under development for Alzheimer's disease, suggesting that there are ongoing efforts to find more effective treatments. However, the specifics of these drugs and their mechanisms are summarized in a table (Table 4) referenced in the paper, which likely includes emerging therapies targeting amyloid [2] plaques, tau protein, and other disease mechanisms.

Overall,the pharmacological treatments available today offer limited benefits, mainly in terms of symptomatic relief, but new drug candidates are under investigation to address the disease more effectively.

CONCLUSION

The use of any measure for the clinical assessment of dementia, whether in people with learning disabilities or in the 'normal' population carries with it limitations. Informed knowledge of these limitations allows use scientific choices which enable us to tailor our neuropsychological battery or adopt alternative measures.

Although these limitations may ultimately require compromise, scientific understanding has provided a clearer picture of the course of dementia than ever before. With the advancement of technology, such as MRI and fMRI, and PET [9] and SPET [9] scans, used in conjunction with neuropsychological tests administered at key time points including follow-ups, the clinician is better placed to make a more reliable diagnosis [10] and prognosis than in the past. It is hope that this will also enlighten service providers in widening access to people with learning disabilities who also have dementia.

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