

REVIEW ARTICLE

Understanding Alzheimer's Disease: Risk Factors, Treatment Approaches, Pathophysiology, And Recent Advances in Research and Medications

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and memory loss. This review article provides an overview of AD, focusing on its risk factors, current understanding, treatment approaches, stages, pathophysiology, recent advances, and medications. The article highlights the growing prevalence of AD globally and its impact on individuals, society and need for a comprehensive understanding of the disease to develop effective preventive measures and treatment strategies. The article also discusses the various risk factors associated with AD, including age, genetics, family history, lifestyle factors, and comorbidities. It emphasizes the importance of identifying modifiable risk factors to reduce the incidence and progression of the disease. Current understanding and treatment approaches for AD are explored, including cognitive interventions, pharmacological therapies, and non-pharmacological approaches such as lifestyle modifications. The pathophysiology section outlines the key pathological hallmarks of AD, including amyloid-beta plaques, neurofibrillary tangles, and synaptic dysfunction. It discusses the role of inflammation, oxidative stress, and neuroinflammation in disease progression. Recent advances in AD research are presented, focusing on emerging biomarkers, imaging techniques, and genetic studies that contribute to early diagnosis and targeted therapies. The article also explores promising avenues such as immunotherapy and precision medicine approaches. Finally, a comprehensive overview of medications commonly used in AD management is provided, including cholinesterase inhibitors and NMDA receptor antagonists. The article highlights their mechanisms of action, effectiveness, and potential side effects.

Key words Alzheimer's disease, Dementia, Amyloid Beta (A β), MRI,

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INTRODUCTION

Alzheimer's disease is a progressive neurological disorder that affects memory, thinking abilities, and behaviour. It is one of the most prevalent and challenging health conditions of our time. First described by German psychiatrist and neuropathologist Alois Alzheimer in 1906, the disease has since gained significant attention due to its devastating impact on individuals, families, and society as a whole [1]. Alzheimer's disease primarily targets the brain, leading to the gradual deterioration of neurons, which are responsible for transmitting messages within the brain and maintaining cognitive function. The formation of abnormal structures, such as amyloid plaques and neurofibrillary tangles, disrupts the normal functioning of neurons, causing their eventual death and the progressive loss of brain tissue [2]. The onset of Alzheimer's disease is characterized by mild memory loss and difficulties in recalling recent events or information. As the disease progresses, individuals may experience confusion, disorientation, and problems with language and problem-solving. Changes in mood, personality, and behaviour, including irritability, anxiety, or withdrawal, are also common. In the later stages of the disease, individuals often require full-time care as they lose the ability to perform basic tasks independently, such

as eating, dressing, and bathing. Alzheimer's disease is ultimately fatal, with individuals typically surviving an average of eight to ten years after diagnosis, although the disease's progression can vary from person to person [2].

Risk Factors

While the exact cause of Alzheimer's disease remains unknown, researchers have identified several risk factors associated with its development. Advanced age is the most significant risk factor, with the incidence of the disease increasing exponentially after the age of 65. Family history and genetic factors, such as certain gene mutations, also contribute to the risk of developing Alzheimer's [3].

Furthermore, certain lifestyle factors have been linked to an increased risk of developing the disease. These include a sedentary lifestyle, poor cardiovascular health, obesity, diabetes, and smoking [4]. However, it is essential to note that having one or more risk factors does not guarantee the development of Alzheimer's disease, as many individuals without any apparent risk factors can still develop the condition.

Current Understanding and Treatment

Researchers and scientists have made significant progress in understanding Alzheimer's disease, but a definitive cure or preventive measure remains elusive. Current treatments primarily focus on managing symptoms and slowing down the progression of the disease. Medications such as cholinesterase inhibitors (e.g., donepezil, rivastigmine, galantamine) and memantine are commonly prescribed to enhance memory and cognitive function [5][6].

Non-pharmacological interventions have also shown promise in improving quality of life and slowing cognitive decline in individuals with Alzheimer's disease. Cognitive stimulation therapy, physical exercise, and social engagement are among the non-pharmacological approaches that have demonstrated positive effects [7][8].

Ongoing research is exploring new avenues for the treatment of Alzheimer's disease. Immunotherapy, which involves using antibodies to target and remove amyloid plaques in the brain, has shown potential in clinical trials [9]. Gene therapy approaches are also being investigated to target specific genetic factors associated with Alzheimer's disease [10].

While a definitive cure or preventive measure is not yet available, the continuous efforts of researchers and scientists provide hope for future breakthroughs in the understanding and treatment of Alzheimer's disease.

Impact on Individuals and Society

Alzheimer's disease not only has a significant impact on affected individuals but also imposes a wide range of effects on their families, caregivers, and society as a whole. Providing care for individuals with Alzheimer's places a considerable burden on family members and caregivers, both emotionally and physically. It can also lead to financial strain due to the high costs associated with medical care, long-term care, and lost productivity. Moreover, Alzheimer's disease has significant economic implications, both on a personal and societal level. The costs associated with medical treatments, caregiving, and support services can be substantial, affecting individuals, families, and healthcare systems. Additionally, the loss of productivity due to caregivers' reduced ability to participate in the workforce can have broader economic consequences [11]. The global impact of Alzheimer's disease is significant, with millions of people affected worldwide. As the global population continues to age, the prevalence of Alzheimer's is expected to rise, placing an increasing burden on healthcare systems and resources. Addressing this growing challenge requires efforts to improve awareness and understanding of the disease, support research initiatives to advance our knowledge and develop effective treatments, and implement comprehensive care strategies to support individuals and their families [12].

Stages of Dementia

Early Stage

- The initial phase of a disease is frequently disregarded, particularly by relatives and friends, and occasionally even by professionals, who perceive it as a natural consequence of aging. As the onset of the illness is gradual, it can be challenging to pinpoint precisely when it commences.
- Developing forgetfulness, particularly concerning recent occurrences, is a notable aspect of this condition.
- Some individuals may encounter challenges in communication, such as experiencing difficulty in retrieving the right words to express themselves.
- Experience disorientation or confusion in familiar surroundings.
- Have trouble keeping track of time, including the current time of day, month, year, or season.
- Encounter challenges in making decisions and managing personal finances.

- Exhibit changes in mood and behavior, such as decreased activity and motivation, loss of interest in activities and hobbies, and potential symptoms of depression, anxiety, or mood swings.
- Occasionally display unusual or uncharacteristic outbursts of anger or aggression.

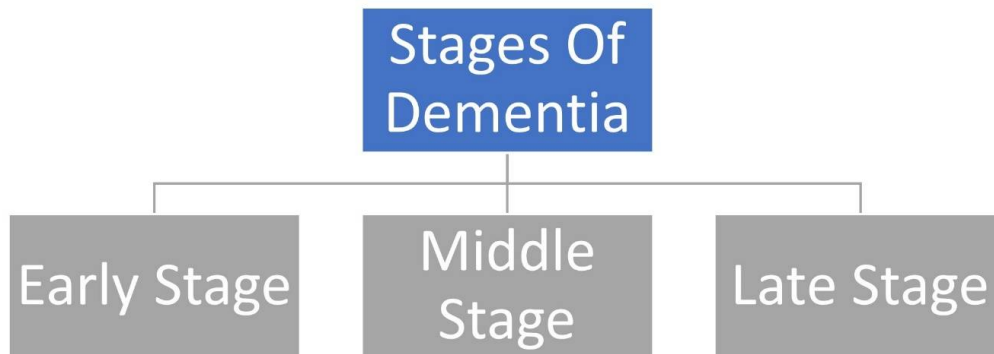


Figure 1: Stages of dementia

Middle stage

As the disease progresses, the limitations become more evident and restrictive:

- Experience significant and pervasive memory loss, particularly regarding recent events and people's names.
- Struggle to comprehend and keep track of time, dates, locations, and events, leading to a potential risk of getting lost both at home and in the community.
- Face increasing difficulties in communication, including challenges with speech and comprehension.
- Require assistance with personal care activities such as toileting, bathing, and dressing.
- Become unable to perform essential tasks like cooking, cleaning, and shopping.
- Depend on substantial support to live safely, as living alone becomes impractical.
- Exhibit behavioural changes like wandering, repetitive questioning, calling out, clinging to others, disrupted sleep patterns, and experiencing hallucinations (seeing or hearing things that are not real).
- May demonstrate inappropriate behaviour both at home and in public settings, such as disinhibition and aggression.

Late stage

- In the final stage, individuals with the disease experience a state of nearly complete dependence and inactivity. The memory disturbances reach a severe level, and the physical manifestations of the disease become more apparent.
- In the advanced stage of the disease, individuals typically lack awareness of time and place. They struggle to comprehend their surroundings and may have difficulty understanding what is happening around them.
- The ability to recognize relatives, friends, and familiar objects diminishes or is completely lost. They require assistance to eat and may experience swallowing difficulties.
- There is an increasing reliance on others for activities of daily living, such as bathing and toileting. Bladder and bowel incontinence may occur.
- Mobility undergoes significant changes, with individuals being unable to walk independently and potentially becoming confined to a wheelchair or bed.
- Behavioural changes may escalate and can include aggression towards caregivers, as well as nonverbal agitation expressed through actions like kicking, hitting, screaming, or moaning.[13]

Pathophysiology

The pathophysiology of Alzheimer's disease (AD) is characterized by a complex interplay of various pathological features that lead to the progressive degeneration and dysfunction of brain cells. While the precise mechanisms underlying AD are not fully understood, several key pathological features have been identified. Here is an overview of the pathophysiology of Alzheimer's disease:

Amyloid Beta (A β) Pathology

a. Amyloid Precursor Protein (APP) Processing: Normally, APP is cleaved by enzymes called secretases to produce soluble forms of A β . In AD, there is an imbalance between the production and clearance of A β , leading to the accumulation of A β plaques in the brain.

b. A β Aggregation: A β peptides have a propensity to aggregate and form insoluble plaques, which are toxic to neurons. These plaques disrupt neuronal communication and contribute to neurodegeneration.

Tau Pathology

a. Hyperphosphorylation of Tau: Tau is a protein that helps stabilize microtubules within neurons. In AD, abnormal phosphorylation of tau leads to the formation of neurofibrillary tangles. These tangles impair the normal functioning of neurons, disrupt intracellular transport, and contribute to neuronal cell death.[14][15]

Neuroinflammation

a. Activation of Microglia: Microglia, the immune cells of the brain, become activated in response to the presence of A β plaques and neurofibrillary tangles. Activated microglia release inflammatory molecules and reactive oxygen species, leading to chronic neuroinflammation.

b. Cytokine Release: Inflammatory molecules such as cytokines and chemokines are released, further exacerbating neuronal damage and promoting neurodegeneration.

Synaptic Dysfunction

a. Disruption of Neurotransmission: A β plaques and neurofibrillary tangles disrupt the normal functioning of synapses, impairing neurotransmission and synaptic plasticity. This results in cognitive deficits, including memory loss and other cognitive impairments.

Oxidative Stress

a. Accumulation of Reactive Oxygen Species (ROS): A β aggregates and neuroinflammation lead to the production of reactive oxygen species, causing oxidative damage to neurons. Oxidative stress further contributes to neurodegeneration and cognitive decline.

Neurovascular Dysfunction

a. Impaired Cerebral Blood Flow: AD is associated with impaired cerebral blood flow regulation and reduced delivery of oxygen and nutrients to the brain. This compromises neuronal function and contributes to the progression of the disease.

Excitotoxicity

a. Glutamate Dysregulation: Excessive release of the neurotransmitter glutamate, accompanied by impaired clearance, leads to excitotoxicity, causing neuronal damage and cell death.

Neurogenesis and Synaptic Plasticity Impairment

a. Reduced Neurogenesis: In AD, neurogenesis, the process of generating new neurons, is impaired, particularly in the hippocampus, a brain region crucial for memory formation.

b. Disruption of Synaptic Plasticity: AD disrupts the mechanisms underlying synaptic plasticity, impairing the ability of synapses to adapt and strengthen connections, leading to memory and cognitive impairments.[16],[17]

Recent advances in Alzheimer's disease

Aducanumab approval: In June 2021, the U.S. Food and Drug Administration (FDA) granted accelerated approval for aducanumab (marketed as Aduhelm) for the treatment of Alzheimer's disease. Aducanumab is an antibody therapy designed to target and remove amyloid-beta plaques in the brain.[18],[19].

Blood-based biomarkers: Researchers have been investigating the use of blood-based biomarkers for Alzheimer's disease. Recent studies have shown promising results in detecting Alzheimer's-related changes through blood tests that measure levels of specific proteins, such as tau and amyloid-beta.[20]

Combination therapies: There has been a growing interest in exploring combination therapies for Alzheimer's disease. Researchers are investigating the potential benefits of combining different drugs or treatment approaches to target multiple pathways involved in the disease, aiming for greater efficacy.[21]

Genetic research: Advances in genetic research have identified several genetic risk factors associated with Alzheimer's disease. The discovery of rare genetic variants and the role of specific genes, such as APOE and TREM2, have provided insights into disease mechanisms and potential targets for therapeutic intervention.[22]

Artificial intelligence (AI) and machine learning: AI and machine learning techniques are being employed to analyze large datasets and identify patterns or biomarkers associated with Alzheimer's disease. These technologies have the potential to aid in early detection, diagnosis, and disease monitoring.[23]

Lifestyle interventions: Lifestyle factors such as exercise, diet, cognitive engagement, and social interaction have been linked to a reduced risk of Alzheimer's disease. Recent research has further emphasized the importance of these interventions in promoting brain health and potentially delaying the onset or progression of the disease.[24]

Diagnosis

➤ Diagnosis criteria

➤ Detection method

Diagnosis criteria

The diagnostic process for Alzheimer's disease involves several steps. Firstly, the patient's medical history should include information from a reliable informant, such as a person close to the patient who can provide additional details. Additionally, a mental state assessment should be conducted, which may involve validated cognitive function tests. The physical examination should focus on identifying vascular and neurological signs, and further investigations should be carried out based on the patient's history and clinical findings.

Assessing dementia requires a two-step process in most cases. Initially, it is crucial to differentiate dementia syndromes from other conditions that can mimic them, such as depression, delirium, or mild cognitive impairment. Distinguishing these conditions is important to ensure an accurate diagnosis. Once a dementia syndrome is recognized, determining the subtype becomes important as it may influence the available treatment options.

In general practice, cognitive screening often involves using the clock test due to its non-confrontational nature. The normal drawing of a clock can provide an indication of the absence of significant cognitive impairment. However, it is important to note that scoring the test can be complex, and relying solely on a single cognitive test for screening may not capture the full range of symptoms and indications associated with the clinical syndrome of dementia. Assessing the patient's activities of daily living alongside cognitive function is also important. It is worth mentioning that there is variability in the assessment instruments used for this purpose.[25]

Detection methods

Neuroimaging has emerged as a promising and rapidly evolving field in the detection of Alzheimer's disease. Various brain imaging techniques, such as PET, MRI, and CT scans, can be utilized to identify abnormalities in the brain and its associated regions. Each scan employs a unique methodology and is capable of detecting specific structures and irregularities within the brain. While brain imaging is not currently a standard component of Alzheimer's disease testing, recent clinical studies have shown encouraging results that may influence the diagnostic process followed by physicians. These advancements have the potential to change how the disease is diagnosed in the future. Despite extensive and effective research over the years, there is currently no definitive treatment available for Alzheimer's disease, which is the most prevalent form of dementia. It has become increasingly evident that early detection of the disease, potentially even before the onset of symptoms, is crucial for successful treatment. Therefore, there is a pressing need for reliable diagnostic methods that can facilitate the initiation of early interventions aimed at slowing down or preventing the progression of the disease. In order to accurately treat Alzheimer's disease, it is imperative to identify it as early as possible. This underscores the importance of developing dependable diagnostic approaches that enable the timely implementation of appropriate treatment strategies. The detection method are shown in (figure no 2).

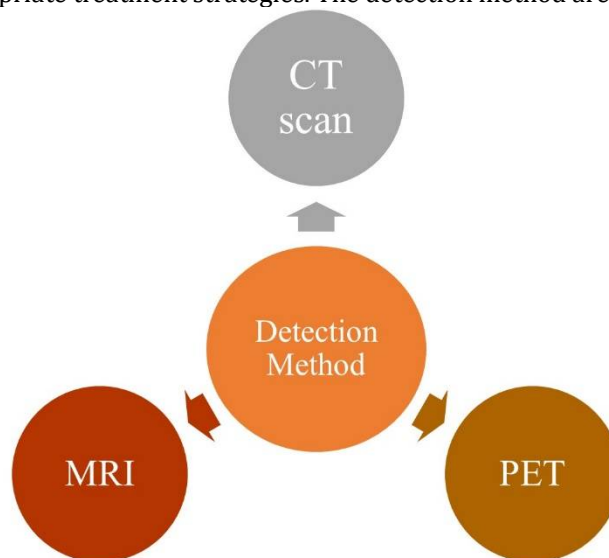


Figure 2: Detection Method

Positron emission tomography (PET)

Positron emission tomography (PET) is a medical imaging technique that utilizes radiation signals to generate a three-dimensional colour image of the human body. In PET imaging, a radiotracer is administered to the patient, which consists of a radioactive substance combined with a naturally occurring chemical. In the case of studying Alzheimer's disease, glucose is commonly used as the chemical.

Once injected, the radiotracer travels to the organs that utilize the specific molecule (glucose in this case) for energy. As the compound is metabolized, it emits positrons, which are positively charged particles. The PET scanner detects the energy emitted by these positrons and converts it into an image displayed on a screen. The resulting PET image provides information about the function of the patient's body by illustrating how effectively the radiotracer is being broken down. The different amounts of positron energy emitted are represented by various colors and intensities in the image, reflecting the level of brain activity.

By analyzing the PET scan, healthcare professionals can identify changes in metabolism, blood flow, and cellular communication processes occurring within the brain. This allows them to assess brain function and detect abnormalities or irregularities associated with diseases such as Alzheimer's. PET imaging provides valuable insights into the inner workings of the brain and aids in diagnosis, treatment planning, and monitoring of various neurological conditions.[26]

Computed tomography (CT)

A computed tomography (CT) scan is a medical imaging technique that captures a series of cross-sectional images of the body. These individual scans are then combined and integrated by a computer to generate a detailed and comprehensive image. A CT scan is valuable in providing physicians with information about tissue density throughout the body, including different regions of the brain. By analysing the density of tissues, doctors can identify abnormalities, such as tumours, lesions, or areas of inflammation.

In some cases, to enhance the clarity of the CT scan, a contrast dye may be administered. This dye is typically injected into the patient's bloodstream, and it helps to create a clear distinction between similar tissues. The contrast dye highlights specific areas of interest, making them more visible and easier to analyse in the CT scan images.

The integration of multiple cross-sectional images allows healthcare professionals to visualize the body and its structures in great detail, facilitating accurate diagnosis and treatment planning. CT scans are commonly used in various medical fields, including neurology, oncology, and orthopedics, among others. They provide valuable insights into the internal structures and help guide medical interventions.[27]

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) is a medical imaging technique that was first introduced in 1977. It utilizes a strong magnetic field and radio waves to generate detailed two or three-dimensional images of the body, aiding in the diagnosis of injuries and illnesses. The key component of an MRI system is the superconducting magnet. This magnet produces a powerful and stable magnetic field that is essential for the functioning of the MRI. The magnetic field aligns the hydrogen atoms within the body's tissues. During an MRI scan, the patient lies inside the MRI machine, which consists of a tube surrounded by the superconducting magnet. Radio waves are then directed at the patient's body, causing the aligned hydrogen atoms to emit signals. These signals are picked up by receivers in the MRI machine and processed by a computer to create detailed images. The resulting MRI images provide excellent anatomical detail and can differentiate between different types of tissues in the body. This enables healthcare professionals to identify abnormalities such as tumors, injuries, or internal organ damage. MRI is a versatile imaging technique that does not use ionizing radiation, making it a safe option for many patients. It is particularly useful in examining soft tissues, such as the brain, spinal cord, muscles, and joints. Additionally, MRI can provide valuable functional and physiological information, allowing doctors to assess blood flow, brain activity, and other dynamic processes.[28] Researchers can assess its effectiveness in detecting structural changes and cellular death in the brains of individuals with Alzheimer's disease. One common observation in Alzheimer's disease is the atrophy or shrinkage of the hippocampus, which can be detected using MRI even before the onset of clinical symptoms. MRI scans are capable of capturing detailed images of the brain's anatomy. By comparing MRI scans of individuals with Alzheimer's disease to those without the condition, researchers can identify changes in the size and structure of brain regions, including the hippocampus. The hippocampus is a region of the brain crucial for memory formation and consolidation. In Alzheimer's disease, this area tends to show early signs of degeneration and atrophy. Researchers can use MRI to measure the volume and shape of the hippocampus, allowing them to track changes over time and compare them to normal patterns. Through

advanced imaging techniques and analysis, researchers can quantitatively assess the extent of hippocampal atrophy in Alzheimer's disease.[29]

Medications in Alzheimer's disease

There are indeed two main types of medication commonly used in the treatment of Alzheimer's disease: acetylcholinesterase inhibitors and N-methyl-D-aspartate (NMDA) antagonists. These medications function through different mechanisms to address the symptoms and progression of the disease.

Acetylcholinesterase inhibitors: These medications, such as donepezil, rivastigmine, and galantamine, work by increasing the levels of acetylcholine in the brain. Acetylcholine is a neurotransmitter involved in memory, learning, and cognitive function. In Alzheimer's disease, there is a decrease in acetylcholine levels due to the degeneration of cholinergic neurons. Acetylcholinesterase inhibitors inhibit the enzyme acetylcholinesterase, which breaks down acetylcholine. By inhibiting this enzyme, more acetylcholine is available to improve communication between brain cells and potentially alleviate cognitive symptoms associated with Alzheimer's disease.[30]

N-methyl-D-aspartate (NMDA) antagonists: The main medication in this class is memantine. NMDA receptors play a role in regulating calcium levels in brain cells and are involved in learning and memory processes. In Alzheimer's disease, there is an excess of glutamate, an excitatory neurotransmitter that stimulates NMDA receptors and can lead to cell damage. NMDA antagonists, like memantine, block the excessive activation of NMDA receptors, helping to regulate the glutamate activity and protect brain cells from further damage. Memantine is typically prescribed for moderate to severe Alzheimer's disease.[31]

CONCLUSION

In conclusion, this review article provides a comprehensive overview of Alzheimer's disease (AD), covering its risk factors, current understanding, treatment approaches, stages, pathophysiology, recent advances, and medications. The article underscores the urgent need for a thorough understanding of AD due to its escalating prevalence and profound impact on individuals and society. By exploring the various risk factors associated with AD, including age, genetics, lifestyle factors, and comorbidities, the article emphasizes the importance of identifying modifiable risk factors to prevent or slow down the progression of the disease. The review highlights the multidisciplinary nature of AD management, encompassing cognitive interventions, pharmacological therapies, and non-pharmacological approaches like lifestyle modifications. The recognition of different stages of dementia in AD, ranging from mild cognitive impairment to severe dementia, allows for a better understanding of disease progression and its implications on cognitive function and daily activities. By elucidating the key pathological hallmarks of AD, such as amyloid-beta plaques, neurofibrillary tangles, and synaptic dysfunction, the article delves into the underlying pathophysiology. It also explores the role of inflammation, oxidative stress, and neuroinflammation in the progression of the disease. The review presents recent advances in AD research, including emerging biomarkers, imaging techniques, and genetic studies that contribute to early diagnosis and targeted therapies. Promising avenues such as immunotherapy and precision medicine approaches hold potential for future breakthroughs in AD treatment. Lastly, the comprehensive overview of medications commonly used in AD management, such as cholinesterase inhibitors and NMDA receptor antagonists, provides insights into their mechanisms of action, effectiveness, and potential side effects. Overall, this review article serves as a valuable resource for healthcare professionals, researchers, and caregivers involved in the understanding, prevention, and management of AD. By consolidating the current knowledge on AD, it contributes to the ongoing efforts to mitigate the burden of this devastating disease and improve the quality of life for individuals affected by AD and their families.

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