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Review Article

Alzheimer's Disease: A Review

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ABSTRACT

The most common cause of dementia in the elderly is Alzheimer's disease. The development of treatments for Alzheimer's disease has been helped by research, at least in part. These achievements and setbacks have sparked discussion over possible gaps in our knowledge of the pathophysiology of Alzheimer's disease as well as possible hazards in the identification of therapeutic targets, development of drug candidates, diagnostics, and clinical trial design. Although there is a lot of clinical and experimental research being conducted, we must accept the likelihood that there won't be a single cure for Alzheimer's disease and that the strategy for developing new drugs to treat this condition needs to be reevaluated. Preclinical research is continuously shedding light on various aspects of the intricate jigsaw that is Alzheimer's disease, and a review of this data may point to patterns of pharmacological interactions rather than specific possible therapeutic targets. We may be getting closer to creating the best possible pharmaceutical strategy for treating Alzheimer's disease thanks to the several encouraging randomized controlled studies that are currently underway and the growing cooperation between pharmaceutical corporations, basic scientists, and clinical researchers. First Off Alzheimer's disease primarily affects the elderly, and as the world's population ages, the illness is becoming more widespread and burdensome on society, the economy, and human resources. There is an urgent need for effective treatments. Although it is still up for debate, current Alzheimer's disease medications improve symptoms by targeting cholinergic and glutamatergic neurotransmission. 1 (table).2- 15 Many substances are in various stages of development, to find medicines that affect disease. We present an up-to-date and thorough overview of the state of medication development for Alzheimer's disease in this review, highlighting therapeutic methods that are still in the preclinical stages and concentrating mostly on substances that are being tested on humans. The main mechanisms of action of drugs are discussed, including those that impact neurotransmission, those that stop misfolded proteins (tau and amyloid β *Aβ+) from building up, and those that repair mitochondrial function or the growth factor balance, among other therapeutic modalities.

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For pragmatic reasons, this subject has historically been divided into specialized discussions of various treatment approaches. We summarize all of the clinical data that are currently available in this paper, discussing them from both a clinical and design standpoint. We also go over general issues related to this subject, such as the underlying dominant hypothesis (one protein, one drug, one disease), its implications, and the necessity of changing it. This theory states that the goal of medication research is to identify a specific substance that affects a single, targeted illness to achieve the intended therapeutic outcomes. A strategy like this, meanwhile, might not be appropriate given how complicated Alzheimer's disease is. cholinergic medications Acetylcholinesterase inhibitors can help restore the reduced cholinergic transmission caused by the early loss of basal forebrain cholinergic neurons, which is a hallmark of the neuropathology of Alzheimer's disease.[1]

INTRODUCTION

Dr. Alois Alzheimer, a German physiatrist and neuropathologist, is credited with being the first to describe a dementing disorder that would later be known as Alzheimer's disease. Alzheimer's disease (AD) is a severe type of dementia that causes impairments in memory, language, and behavior. The World Health Organization (WHO) predicts that by 2050, there will be 114 million patients worldwide, representing a quadrupling of the current prevalence in the population during the next several decades. In addition to having a significant social impact, this would undoubtedly result in an increased financial strain on healthcare systems across the globe. According to estimates, 46.8 million individuals worldwide suffer from dementia, and the cost of dementia care was predicted to be $818 billion in the United States in 2010 **[2].**

The two main pathogenic alterations found in AD brain tissue are hyperphosphorylated tau (tau), a microtubule assembly protein that accumulates intracellularly as neurofibrillary tangles (NFTs), and amyloid-β (Aβ) peptide, which is deposited extracellularly in diffuse and neuritic plaques. Reactive microgliosis and extensive loss of neurons, white matter, and synapses are other alterations. It's yet unclear what precise processes are causing these modifications**.[3]**

Non-Genetic Hazard And Safeguarding Variables:

Cerebrovascular Disease:

The risk of dementia is increased by cerebral vascular abnormalities such as hemorrhagic infarcts, minor and large ischemic cortical infarcts, vasculopathy, and white matter alterations; however, the precise underlying mechanisms are still unknown. The thalamus and the thalamocortical projections are two key brain regions involved in memory function that may be directly damaged by infarcts or white matter hyperintensities. They might, however, also cause more Aβ to be deposited, which could result in cognitive deterioration or trigger inflammatory reactions that compromise cognitive function. Lastly, cyclin-dependent kinase 5 (CDK5), a serine–threonine kinase essential to synaptic plasticity and synapse formation, may become overexpressed as a result of hypoperfusion. (61) Unusual CDK5 activity is linked to neural processes that contribute to the production of NFTs (63), and it may be a crucial protein that connects NFT pathophysiology to amyloid buildup**.[4,5]**

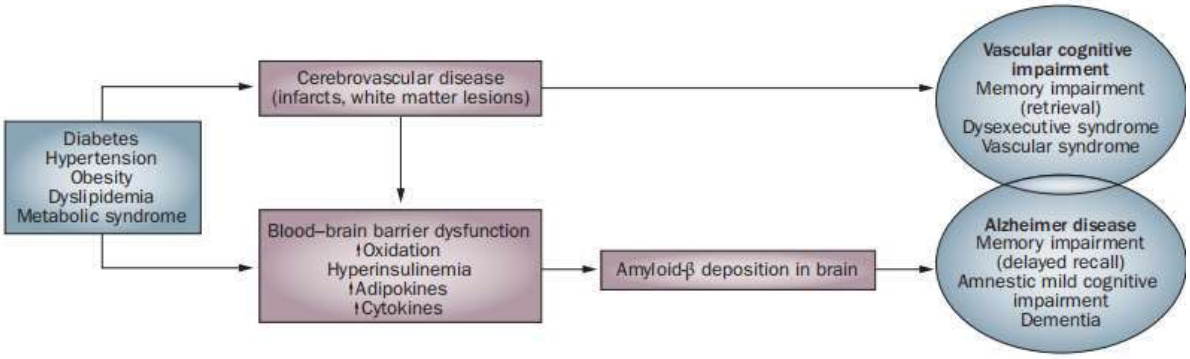


Figure 1 | Potential mechanisms linking vascular risk factors and cognitive impairment. At least two pathways exist that result in cognitive impairment and dementia: development of cerebrovascular disease may lead to vascular cognitive impairment syndromes, and deposition of amyloid-β may lead to other distinct amnestic clinical syndromes, including Alzheimer disease. In addition, these pathways may overlap and interact, resulting in mixed cognitive syndromes.

Blood Pressure:

There is still contradictory data linking blood pressure measurements taken in later life with dementia and cognitive impairment from cross-sectional and longitudinal research. These disputes can be partially ascribed to variations in research methodology, particularly in the interval between blood pressure monitoring and cognitive ability evaluation, as well as in the age range at which these parameters were assessed. Nonetheless, data from observational studies investigating the relationship between high blood pressure in midlife (40–60 years of age) and late-life cognitive impairment have shown to be generally consistent across cohorts, indicating that high blood pressure in midlife does increase the risk of dementia, AD, and later-life cognitive impairment. **[6]** High blood pressure may raise the risk of AD by impacting the vascular integrity of the blood–brain barrier (BBB), which causes extravasation of proteins into the brain.) Protein extravasation can consequently result in cell damage, apoptosis, a decrease in neuronal or synaptic function, and an increase in Aβ buildup, all of which can impair cognitive performance. As people age, the correlation between high blood pressure and the risk of AD decreases or even reverses, with higher blood pressure acting as a preventive measure**.**

This observation could be explained by the fact that blood pressure starts to drop as soon as AD manifests, potentially due to alterations in the autonomic regulation of blood flow, weight loss, and vascular stiffening. There are contradictory results from the randomized, placebo-controlled studies (RCTs) assessing the value of antihypertensive medications in patients with cognitive impairment.**[7]**

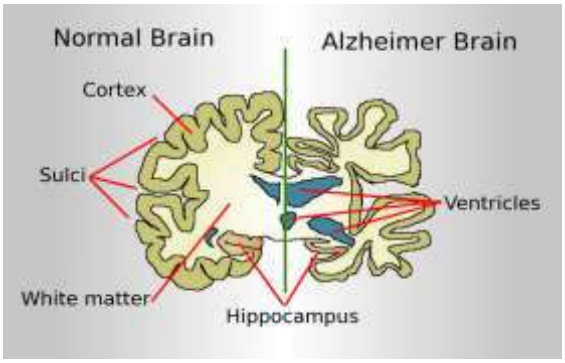


Fig no.2 Alzheimer's Disease

❖ **Alzheimer's Disease Phases :[1]**

Depending on their personalities, each person with Alzheimer's disease will exhibit themselves slightly differently. Although there will be differences in the emotional, behavioral, and cognitive changes as well, researchers and clinicians generally agree that there are broad characteristics described by the stage model**.[8]**

◆ In the **first phase,**

the "forgetfulness phase," there is typically a propensity to forget where objects have been placed and difficulties recalling recent events. In [27] Names of people and places you used to know

may be difficult to remember, and you may continue to feel disoriented overall and have poor short-term memory.**[9]**

- **The second recognized phase**

The term 'confusional phase' refers to the second acknowledged phase. A failing memory is accompanied by a decreasing attention span and a reduction in overall intellectual ability. confusion in the environment, trouble finding words, and other modifications to Speech are visible.**[10]** Complicated jobs are tough to complete, and occasionally they are done incorrectly or clumsily. and frequently the last talents acquired will be lost fastest. The absence of enthusiasm for news and surroundings can be about fast and can cause a great deal of distress to family members and pals. **[11]**

- **The third phase:**

The 'dementia phase', which is the third stage, is marked by a person's behavior that seems disorganized and occasionally odd due to a loss of purpose. People in this phase experience further declines in their memory, calculation skills (dyscalculia), and language-related abilities, necessitating continuous supervision of their remaining intellectual and self-care capacities. are negatively impacted and ultimately lost. Self-care skills require ongoing assistance. such as for feeding, clothing, grooming, and using the restroom[**12**]. Physical wasting that occurs gradually can also be visible, indicating assistance with walking. Occasionally, the first year or two of life will proceed till they pass away in a nearly vegetative condition. Environmental elements could play a part in causing Alzheimer's in those who are vulnerable. A correlation between Alzheimer's disease illness and aluminum has been developed for seven years.**[13]**

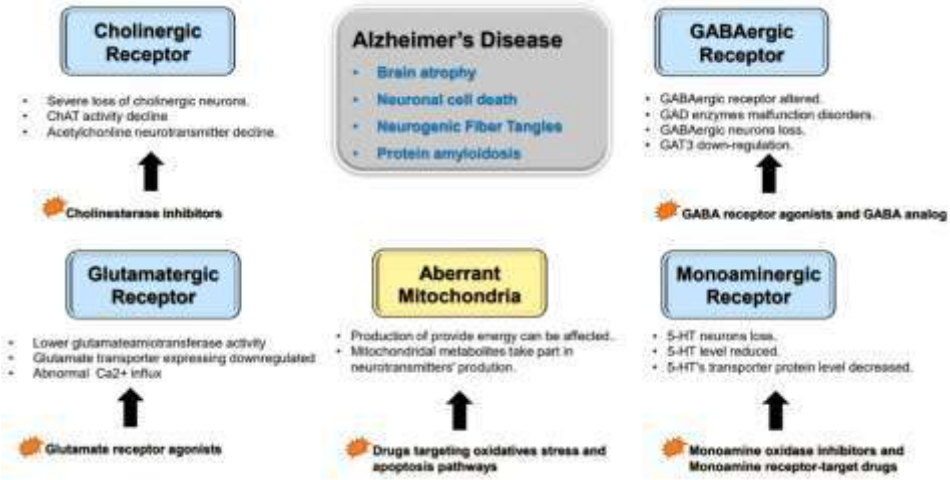


Fig.no.3 Description of Alzheimer's Disease.

Prevention:

There is now no recognized cause of Alzheimer's disease, hence there is no surefire method to ward against the illness. However, leading a healthy lifestyle can lower your risk.[**14**]

Lowering your chance of heart problems:

Alzheimer's disease and vascular dementia have been associated with a higher risk of cardiovascular disease. By making improvements to your cardiovascular health, you may be able to lower your risk of having these disorders as well as other dangerous issues including heart attacks and strokes.

These include:

- giving up alcohol.
- eating a nutritious, balanced diet that includes at least five servings of fruit and vegetables each day.

- quitting smoking.
- engaging in moderate-intensity aerobic exercise, such as brisk walking or cycling, for at least 150 minutes per week, or as long as you can.**[15]**

- **Other Risk Factors For Dementia:**

Recent studies indicate that additional variables may also be significant, albeit this does not imply that these variables cause dementia in and of themselves.

Among them are:

- hearing loss
- Untreated depression (but this may potentially indicate a dementia sign)
- Being alone or socially isolated
- leading a sedentary life

The study concluded that we could drastically lower our risk of dementia by making changes to every risk factor that we have control over.

Staying mentally and socially active:

Some data suggest those who maintain a high level of mental and social activity throughout their lives have lower rates of dementia.

You may be able to lower your risk of dementia, including Alzheimer's disease, by doing the following:

• reading
• acquiring a foreign language
• Performing on an instrument
• Participating in community service locally
• Participating in team sports like bowling
• attempting novel pastimes or pursuits
• continuing to lead a socially active life

Research has not yet established if interventions like "brain training" computer games can help prevent dementia, but they have been found to improve cognition over a brief period.**[16]**

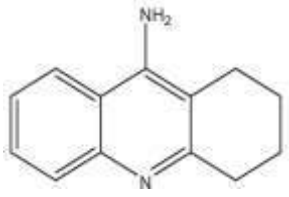
Treatment:

Cholinesterase Inhibitors:

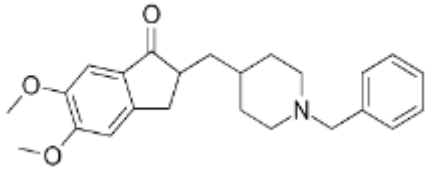
The cholinergic hypothesis states that decreased acetylcholine (ACh) production causes AD. Inhibiting acetylcholinesterase (AChE) is one way to raise cholinergic levels, which is thought to improve brain and neuronal cell function. Acetylcholine breakdown at synapses is inhibited by AChEIs, causing a continual build-up of ACh and activation of cholinergic receptors. Tetrahydroaminoacridine, or tacrine.

The first cholinesterase inhibitor medication approved by the FDA (Food and Drug Administration) for the treatment of AD was (1, Figure 4). It works by increasing ACh in muscarinic neurons. However, it was quickly taken off the market due to a high rate of side effects, such as hepatotoxicity, and a lack of benefits, which were noted in multiple trials. Subsequently, several AChEIs were developed and are now being used to treat AD symptoms. These include galantamine (4, Figure 4), rivastigmine (3, Figure 4), and donepezil (2, Figure 4). **[17,18,19,20].** Increasing choline reuptake and acetylcholine production at the presynaptic terminals is another method that may be useful in the treatment of AD. Targeting the choline transporter (CHT1) will help achieve this.[**21]**

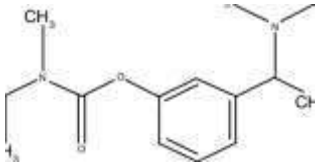
The structure of some compounds is as follows:



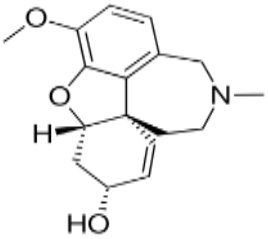
(1) Tacrine



(2) Donepezil



(3) Rivastigmine



(4) Galanatamine

Figure 4 shows the chemical structures of the medications that are authorized to treat AD symptoms: tacrine1, donepezil2, rivastigmine3, and galantamine4.

Alzheimer's Disease Risk Factor:

Age:

Aging is the primary risk factor for AD. Rarely do younger people have this illness, and most occurrences of AD begin later in life, after the age of 65 [**22**]. The process of aging is intricate and unchangeable, affecting several organs and cell systems, and culminating in a decline in brain function. volume and weight, degeneration of synapses, and localized swelling of the ventricles along with NFT and SP deposition. Additionally, as people age, several diseases could develop, including hyperglycemia, mitochondrial malfunction, dyshomeostasis of cholesterol, hypometabolism, and cognitive back-off. It challenging to differentiate between the cases in which these changes occur and those that are typical of aging. initial AD **[23,24].** Age-based classification of AD distinguishes early-onset AD (EOAD), an uncommon form, from other forms. 1-6 percent of cases, the majority of which are familial AD cases defined by having more than one person with AD across multiple generations; the age range is between 30 and 60 or 65.

The subsequent form is known as late-onset AD (LOAD), and it is more prevalent in people whose onset ages are over 65. Both kinds may manifest in individuals with a positive family history of AD and in families with a late-onset illness **[25].**

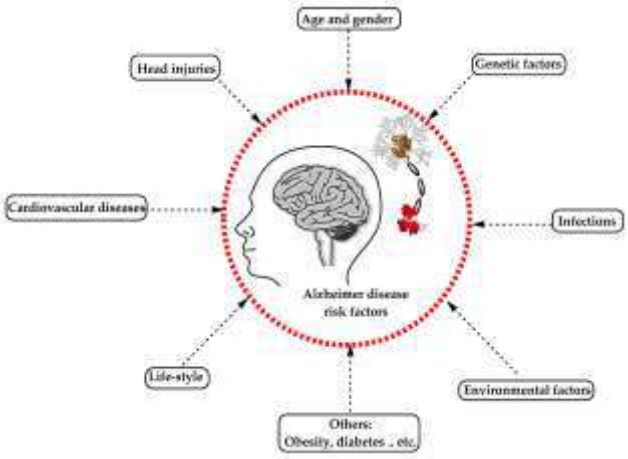


Figure 5: The risk factors for Alzheimer's disease.

Genetics:

Over time, it was established that genetic factors were a major contributing element to the development of AD. Genetic factors were implicated in 70% of AD cases: most EOAD cases are passed down through an autosomal dominant pattern, and changes to the dominant genes, like Apolipoprotein E, Amyloid Prototype Protein (APP), Presenilin-1 (PSEN-1), and Presenilin-2 (PSEN-2) (ApoE) have been linked to AD [**26,27].** We go over the significant genetic risk factors for AD here.

Theory of Alzheimer's Disease:

Cholinergic Hypothesis:

The manufacture of acetylcholine (ACh) is carried out by the enzyme choline acetyltransferase (ChAT), which was linked to abnormalities in neocortical and presynaptic cholinergic function in the 1970s. Given that ACh is crucial for cognitive function, the cholinergic hypothesis of AD was put forth. Choline and acetyl-coenzyme A are

combined in the cytoplasm of cholinergic neurons to produce ACh. via the vesicular acetylcholine transporter and the ChAT enzyme, respectively, to the synaptic vesicles.Figure 3: (VAChT). ACh plays a role in the brain in several physiological functions, including memory, learning, sensory data, focus, and other vital processes. The cholinergic system degenerating It was discovered that AD causes neuronal changes that affect memory and cognitive function. B-amyloid is thought to impact cholinergic neurotransmission and to result in the decrease of research showed that amyloid and cholinergic synaptic loss is linked to cholinergic synaptic uptake and ACh release. Fibril production is associated with the neurotoxicity of Aβ oligomers and the interactions between AChE and Aβ.protein. The development of AD is also influenced by other factors, such as a decrease in nicotine.

With the deficiency in excitatory amino acid (EAA) neurotransmission, glutamate concentration and D-aspartate absorption are markedly decreased in many cortical areas in AD brains. M2 Ach receptors are found on presynaptic cholinergic terminals. This is on top of the application of antagonists of cholinergic receptors, such as scopolamine, which have been shown to cause amnesia. This result can be stopped by using substances that stimulate the production of acetylcholine **[28,29]**

The cholinergic hypothesis is therefore predicated on three ideas: diminished presynaptic cholinergic markers in the cerebral cortex; severe neurodegeneration of the basal forebrain's nucleus basalis of Meynert (NBM), the source of cortical cholinergic innervation; and the function of cholinergic antagonists have the opposite effect on memory deterioration as agonists do [**30].**

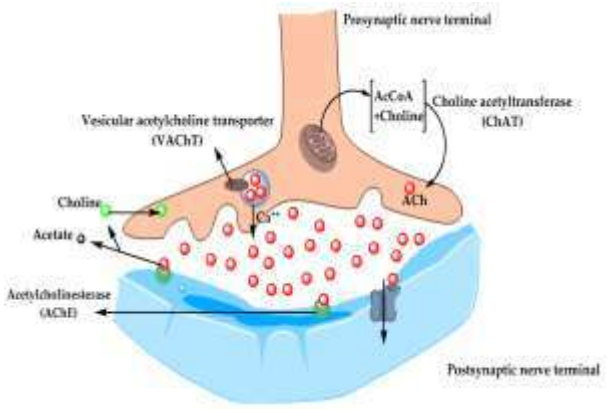


Figure 6: The process through which acetylcholine is synthesized and transported between presynaptic and post-synaptic nerve terminals.

Amyloid Hypothesis:

The amyloid hypothesis originated from the long-standing recognition for decades that dementia is strongly correlated with aberrant deposition of β-sheets in the central nervous system. However, it was discovered that as people age, amyloid plaques (AP) can also accumulate in normally healthy brains. It prompted the question of whether or not AD onset is caused by AP deposition. Consequently, Other theories about the non-inherited form of AD (NIAD) have been put forth recently. Nonetheless, the amyloid hypothesis is still the most widely recognized pathogenic mechanism for hereditary IAD or AD. According to the amyloid hypothesis, Aβ, which is generated from APP by β- and Aging or disease-related factors reduces γ-secretase, which causes Aβ to build up. Proteases (Aβ40) plus Aβ42). An increase in the Aβ42/Aβ40 ratio causes the production of Aβ amyloid fibrils. causing neurotoxicity and the formation of tau pathology, which in turn causes neuronal cell neurodegeneration and death. Risk factors for AD and mutations in many genes, including APP, PSEN1, and PSEN2 have been shown to impact the anabolism and catabolism of Aβ, which quickly leads to a buildup of Aβ and rapid neurodegenerative development [**31].**

Tests:

Diagnosing Alzheimer's disease would likely include the following tests:

neurological and physical examination:

A physical examination will be conducted by a medical practitioner. Testing for reflexes is one possible component of a neurological evaluation.

• Tone and strength of muscles.

• The ability to go across the room and get out of a chair.

• The ability to see and hear.

• Arrangement.

• Harmony.

Laboratory tests:

Blood tests can assist in ruling out additional possible reasons for confusion and memory loss, such as low vitamin levels or thyroid disorders. Tau and beta-amyloid protein levels can also be determined by blood tests, however, their availability and coverage may be restricted.[32]

Psychological state and neuropsychological evaluations

A quick mental status exam may be administered by your healthcare provider to evaluate your memory and other cognitive abilities. Extended versions of this kind of examination might offer additional information about mental functioning that is comparable to individuals with comparable age and educational attainment. These examinations can aid in the diagnostic process and act as a springboard for further symptom monitoring.

Brain imaging

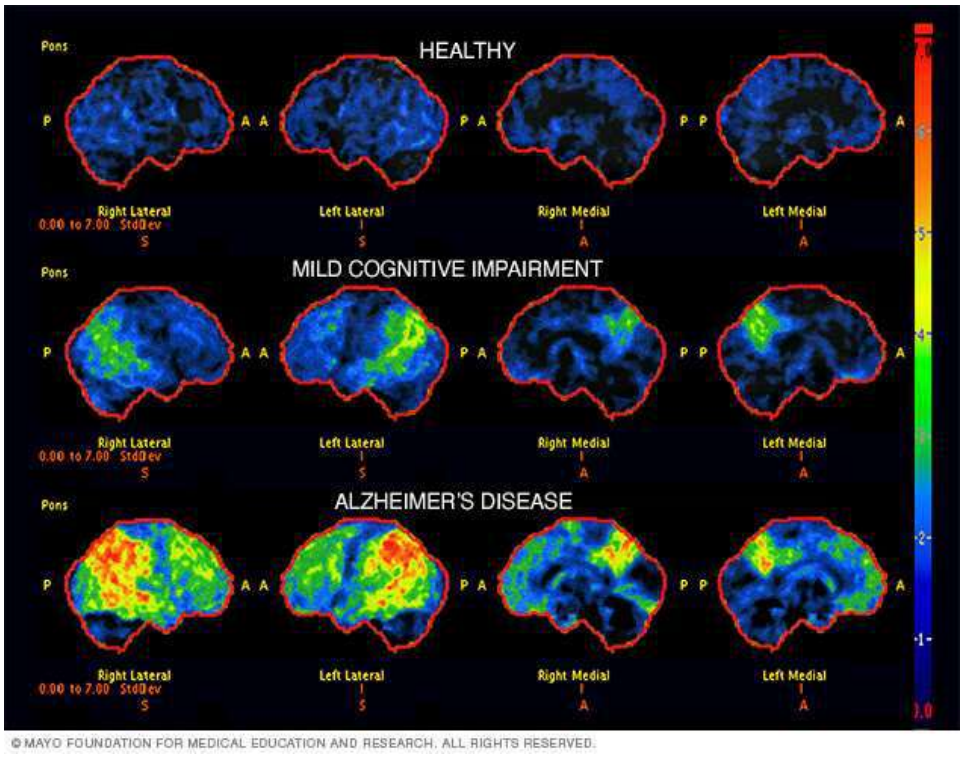


Fig.no.7 Brain scan images for diagnosis of Alzheimer's disease

Brain imaging is commonly used to identify visual abnormalities associated with diseases other than Alzheimer's disease that may present with similar symptoms, such as strokes, trauma, or tumors. While new imaging techniques are mostly utilized in clinical trials or large medical centers, they may be useful in detecting specific brain alterations associated with Alzheimer's disease.[33]

• **MRIs, or magnetic resonance imaging**:

A strong magnetic field combined with radio waves allows MRI to create precise images of the brain. MRI scans rule out other illnesses while also potentially revealing Alzheimer's disease-related

shrinkage in specific brain regions. In most cases, an MRI is better than a CT scan for assessing dementia.

• CT, or computerized tomography:

The specialist X-ray technology known as a CT scan creates cross-sectional images of your brain. Usually, it's used to rule out brain injuries, strokes, and malignancies. Using Positron Emission Tomography (PET), illness processes can be visualized through images. A low-level radioactive tracer is injected into the blood during a PET scan to highlight a specific brain feature. PET imaging could show:

PET scans using fluorodeoxyglucose (FDG):

reveal brain regions with low food metabolism. Distinguishing Alzheimer's disease from other forms of dementia can be made easier by looking for patterns in the areas with reduced metabolism.

• The amount of amyloid deposits in the brain can be quantified by amyloid PET imaging. This test may be utilized if a person exhibits atypical or very early onset dementia symptoms, albeit it is primarily employed in research.

• In a research environment, tau PET imaging is typically utilized to evaluate brain tangles.

In certain situations, measurements of tau and amyloid in the cerebrospinal fluid may be made using alternative methods. If someone is experiencing dementia at an earlier age than usual or if symptoms are getting worse quickly, this may be done.

Future diagnostic tests:

upcoming diagnostic examinations

Tests that can quantify biological indicators of disease processes in the brain are being developed by researchers. These examinations, which include blood testing, could increase diagnosis precision. They might also make it possible to diagnose the illness before symptoms appear. Currently, a blood test to determine beta-amyloid levels is available. For the majority of patients undergoing an Alzheimer's disease evaluation, genetic testing is not advised. However, those who have a family history of early-onset Alzheimer's disease could give it some thought. To discuss the advantages and disadvantages of a genetic test, schedule a meeting with a genetic counselor.[34]

CONCLUSION

FINAL SAY There are limitations to using any metric for the clinical assessment of dementia, whether it is in the "normal" population or individuals with learning impairments. Knowledgeable Understanding these constraints enables us to make scientific decisions that allow us to customize our neuropsychological battery or use different strategies. In the end, these constraints might lead to a compromise; however, scientific Our understanding of the progression of dementia is now better than it has ever been. Along with technology advancements like fMRI and MRI as well as PET and SPET scans, which are used in addition to neuropsychological assessments given at crucial junctures, such as follow-ups, the doctor is in a better position to provide a more trustworthy diagnosis and prognosis than in the historical. We're hoping that this will also teach service providers how to reach more people with dementia and learning impairments combined.

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