International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 31, Issue 4, April 2025 **ijppr.humanjournals.com** ISSN: 2349-7203

A Comprehensive Review on Screening Methods of Alzheimer's Disease

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Received: 2025-4-01 Revised: 2025-4-12 Accepted: 2025-4-20

ABSTRACT:

Alzheimer's disease (AD) is the most common type of dementia. It is a progressive disease beginning with mild memory loss and possibly leading to loss of the ability to carry on a conversation and respond tothe environment. It involves parts of the brain that control thought, memory, and, language. It is the most frequent cause of dementia in western societies. In the US, approximately 5.5 million people are affected, and the prevalence worldwide is estimated to be as high as 24 million. The pathogenesis of Alzheimer's disease involves various pathophysiological events, including the accumulation of amyloid and tau, neuro-inflammation, and neuronal injury. Clinical trials focusing on new drugs for AD were documented in 2020, but subsequent developments have emerged. Notably, the US-FDA has approved Aducanumab and Lecanemab, both antibodies targeting amyloid, marking the end of a nearly two-decade period withoutnew AD drugs. Alzheimer's disease is diagnosed by the presence of extracellular amyloid deposits in theform of plaques and intracellular neurofibrillary tangles, in postmortem brains. The amyloid deposits consist mostly of self-aggregating 40 to 43 amino acid residue peptides, Aβ, which are proteolytically derived from a family of 695 to 770 amino acid transmembrane glycoproteins, the amyloid precursor proteins (APP). The molecular pathogenesis of the disease remains unclear, but progress toward identifying therapeutic targets is gaining pace. Studiescarried out on human platelets have shed light on APP and Aβ metabolism and function. Platelets contain large amounts of APP protein at a level comparable to that of brain and Aβ peptides to a lesserextent. Because platelets can generate Aβ and soluble forms of APP by mechanisms similar to those observed in neuronal cells, platelets may be useful in monitoring responses to therapeutic interventions targeted directly or indirectly at APP/Aβ metabolism. The platelet APP isoform ratio has been shownto correlate with the progression of clinical symptoms and cognitive decline in AD, and this ratio couldpotentially be useful as an adjunctive clinical value in the diagnosis of AD, monitoring disease progression, and therapeutic response. The symptoms evokes as the disease get progressed so screening at the early stage is crucial to prevent the progression of disease. The present study is planned to explore the novel drugs and Screenings methods of Alzheimer's disease.

Keywords: Adecanumab, lecanemab, neurofibrillary tangles, diagnostic marker, homeostasis

INTRODUCTION

Alzheimer's disease is named after Dr. Alois Alzheimer. In 1906, Dr. Alzheimer noticed changes in the brain tissue of a woman who had died of an unusual mental illness. Her symptoms included memory loss, language problems, and unpredictable behavior. As modern society ages rapidly, the number of people with dementia is sharply increasing. Direct medical costs and indirect social costs for dementia patients are also increasing exponentially. However, the lack of social awareness about dementia results in difficulties to dementia patients and their families. So, understanding dementia is the first step to remove or reduce the stigma of dementia patients and promote the health of our community. Alzheimer's disease is the most common form of dementia[1]. The term, 'Alzheimer's disease' has been used for over 100 years since first used in 1910. With the remarkable growth of science and medical technologies, the techniques for diagnosis and treatment of dementia have also improved. Although the effects of the current symptomatic therapy are still limited, dramatic improvement is expected in the future through the continued research on disease modifying strategiesat the earlier stage of disease. It is important to look at the past to understand the present and obtain aninsight into the future. In this article, we review the etymology and history of dementia and previous modes of recognizing dementia. We also review the historical developments leading to the terminologyof Alzheimer's disease[2]. The exact causes of Alzheimer's disease aren't fully understood. But at a basic level, brain proteins fail to function as usual. This disrupts the work of brain cells, also called neurons, and triggers a series of events. The neurons become damaged and lose connections to each other. They eventually die.

Scientists believe that for most people, Alzheimer's disease is caused by a combination of genetic, lifestyle and environmental factors that affect the brain over time.. In less than 1% of cases, Alzheimer's is caused by specific genetic changes that almost guarantee a person will develop the disease. In these cases, the disease usually begins in middleage.The development of the disease begins years before the first symptoms. The damage most oftenstarts in the region of the brain that controls memory.The loss of neurons spreads in a somewhat predictable pattern to other regions of the brain. Bythe late stage of the disease, the brain has shrunk significantly.

DISCUSSION

I. Stages of Alzheimer's Disease:

Stage-1:

Alzheimer's disease, there is usually very mild memory loss or problems with thinking abilities. The person may have a hard time remembering where they placed something or havea hard time recalling the right word to say. However, they still are independent, meaning theycan still take care of themselves and do things like driving. During the middle stages of Alzheimer's disease, the cognitive processes get worse. Now the person may not be able to remember their personal history, like their address or phone number.They also may have a hard time recalling memories or remembering something from their past.The person is no longer able to take care of themselves because in this stage, they tend to forgetwhere they are and often have a hard time using the bathroom or getting dressed appropriatelyfor the day. An example of this is the person wearing shorts in the winter. Along with the cognitive changes, the person may begin to feel sad, lonely, anxious, and paranoid. The symptoms vary from person to person.

Stage-2:

They need a caregiver to assist them with their tasks and the caregiving will increase as the diseaseprogresses. However, it's important to help them without trying to do everything for them. They are still adults and they want to be treated as such, so it's important to still let them have at least some control over their life. Whether that's letting them do simply chores, like folding clothes, or doing activities, like arts and crafts. This will help provide a sense of normalcy.

Stage-3:

People begin to lose sense and control of the environment around them. By this point, the cognitive abilities of the individual have tremendously decreased. They can no longer speak in long formulatedsentences, instead they speak in short fragments or words. They have trouble completing everyday tasks like walking, sitting, eating, and drinking. This means that they require around the clock assistance to make sure that they are remembering to eat and to help them eat. In general, the assistanceis meant to make sure the person is safe and is living to their best ability. At this point, the individualsare very susceptible to infections. When the symptoms and daily conditions get really bad, usually, families turn to hospice care, so that the patient is comfortable at the end of their life. Hospice care also provides emotional support to loved ones, which is vital. Losing a loved one can cause serious emotional and mental strain, so that support is important.

Stage-4:

In the final stage, People with alzheimer disease may be unable to talk with family members or knowwhat is going on around them. This disease can't be cured. Healthcare providers and caregivers often focus treatment on slowing the process and ensuring a good quality of life for everyone involved. [3]

II. Progression model of AD:

Introduction: An Alzheimer's disease (AD) dementia disease progression model was developed basedon the integrated Alzheimer's disease Rating Scale (iADRS).

Methods: Data from 3483 placebo participants in six AD trials were used to develop the disease progression model with NONMEM (version 7.4.2) and examined for mild cognitive impairment, andmild and moderate dementia due to AD.

Results: Baseline iADRS score was significantly influenced by AD symptomatic medication use, EXPEDITION2 enrolment (included moderate AD participants), age, and baseline Mini-Mental StateExamination (MMSE) score. Rate of disease progression increased across disease stage and was significantly influenced by AD medication use, age, and baseline MMSE score. Results can help optimize future clinical trial design and aid in understanding treatment effects.[5]

III.SYMPTOMS OF ALZHEIMER'S DISEASE:

 Memory loss: A person may have difficulty taking in new information and remembering information. This can lead to repeating questions or conversations losing objects forgetting about events or appointments wandering or getting lost.

 Cognitive deficits: A person may experience difficulty with reasoning, complex tasks, and judgment. This can lead to a reduced understanding of safety and risks difficulty with money or paying bills difficulty making decisions difficulty completing tasks that have several stages,such as getting dressed.

 Problems with recognition: A person may become less able to recognize faces or objects or less able to use basic tools. These issues are not due to problems with eyesight.

 Problems with spatial awareness: A person may have difficulty with their balance, trip over,or spill things more often, or they may have difficulty orienting clothing to their body when getting dressed.

 Problems with speaking, reading, or writing: A person may develop difficulties with thinking of common words, or they may make more speech, spelling, or writing errors.

 Personality or behaviour changes: A person may experience changes in personality and behaviour that include becoming upset, angry, or worried more often than before a loss of interest in or motivation for activities they usually enjoy a loss of empathy compulsive, obsessive, or socially inappropriate behaviour [6].

IV . ALZHEIMER'S DISEASE PATHOLOGY:

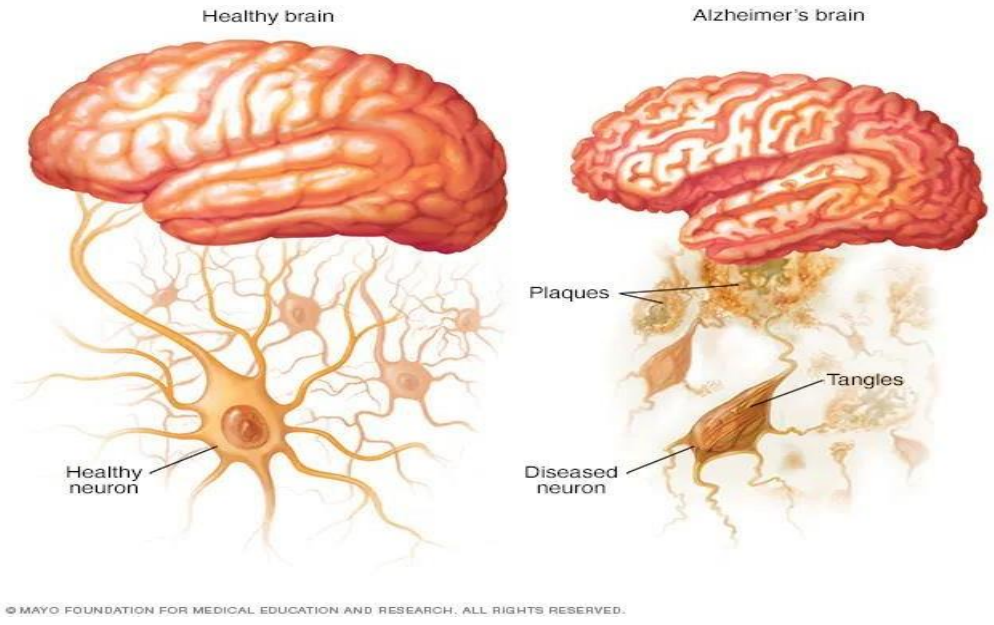

Fig 1 : New Targets of Alzheimer's Disease

Researchers trying to understand the cause of Alzheimer's disease are focused on the role of twoproteins Amyloid and tau

- **Plaques:** Beta-amyloid is a fragment of a larger protein. When these fragments clump together,they appear to have a toxic effect

on neurons and to disrupt communication between brain cells. These clumps form larger deposits called amyloid plaques, which also include other cellular debris.

- **Tangles:** Tau proteins play a part in a brain cell's internal support and transport system to carrynutrients and other essential materials. In Alzheimer's disease, tau proteins change shape and organize into structures called neurofibrillary tangles. The tangles disrupt the transport systemand cause damage to cells.

A. Nicotinic receptor agonism

The cholinergic system is well studied in AD. Neuronal nicotinic receptors (NNRs) for ACh are decreased in the AD brain and this reduction correlates with cognitive impairment. Most NNR agonistscross the blood-brain barrier. NNR agonists improve cognition in small uncontrolled studies of normalvolunteers[18] and AD patients. Animal model studies suggest that these agents are as effective in improving cognitive performance as AChEI therapy. Larger, more well-controlled clinical trials of NNR agonists will inform of their safety and efficacy in AD. No agents have been approved with NNRs as their target. A recent completed trial of one agent, AB-108, failed to meet its cognitive endpoints.

B. GABA receptor agonism and antagonism

As neurons that supply excitatory neurotransmission are lost in AD, inhibitory systems such as gammaaminobutyric acid (GABA) neurotransmission may go unchecked and result in cognitive impairment.There is disagreement in the literature whether GABAergic neurons are less susceptible to the pathology of AD, relative to excitatory neurons, or if levels of the neurotransmitter and both GABA-A and GABA-B receptors are decreased in AD. Regardless, agents that stabilize this system may modulate excitatory tone and reduce excitotoxicity. One selective GABA-B receptor antagonist was clinically investigated in mild cognitive impairment, but subsequently failed to demonstrate efficacy in AD. Alternatively, inverse agonists of the GABA-A receptor benzodiazepine-binding site (believedto reduce synaptic inhibition by reducing chloride ion flux) may enhance cognition.Off target effects such as seizures and anxiety are a concern in compounds with inverse agonist or antagonist propertiesat the GABA receptor. A Phase II clinical trial of etazolate, a GABA-A receptor modulator, recently completed enrollment. The synthetic GABA analog 3-amino-1-propanesulfonic acid (3APS; also known as tramiprosate or Alzhemed), was actively pursued as a treatment for AD, based more on its affinity for Aβ than any GABAergic properties.

C. Serotonergic modulation

Of the 14 different serotonin (5-HT) receptor subtypes, several including 5-HT1A, 5-HT4, and 5-HT6are expressed in areas important to learning and memory and significantly decline in AD. Levels of HTRs may also change in very mild disease, further implicating these receptors in the cognitive impairment associated with AD. 5-HTRs may also be altered in other dementias. The role of the 5- HTRs is complex, including regulation of a variety of other neurotransmitter systems, such as ACh, dopamine, GABA, and glutamate. In line with this complexity, both selective agonists and antagonistsof 5-HTRs have beneficial cognitive effects in animal models. One selective 5-HT1AR antagonist hasreached Phase I investigation in man as a treatment for AD. Results from a Phase II trial of a 5-HT6 antagonist are encouraging.

D. Histamine H3 receptor antagonism

Four subtypes of histamine receptor exist and among them the H3 receptor is highly expressed in human brain, including in areas important to memory function. H3 functions as a presynapticautoreceptor and a postsynaptic heteroreceptor and regulates histamine function as well as release ofa variety of neurotransmitters. Antagonists and inverse agonists of the H3 receptor increase neurotransmitter levels of ACh, dopamine, norepinephrine, and 5-HT. Expression of H3 receptors in the periphery is limited, relative to expression in the brain. Unlike many other receptor systems, H3 receptor levels are maintained through the course of AD progression.

I. PHARMACOLOGICAL TREATMENT OF ALZHEIMER'S DISEASE:

Several prescription drugs are approved by the U.S. Food and Drug Administration (FDA) for Alzheimer's disease to help either manage the symptoms of or to treat the disease. Most FDA-approveddrugs work best for people in the early or middle stages of

Alzheimer's. There are currently no knowninterventions that will cure Alzheimer's[10].

Medications for mild to moderate Alzheimer's disease:

Treating the symptoms of Alzheimer's can help provide people with comfort, dignity, and independence for a longer period of time and also assist their caregivers. Galantamine, rivastigmine, and donepezil are cholinesterase inhibitors that are prescribed for mild to moderate Alzheimer's symptoms. These drugs may help reduce or control some cognitive and behavioural symptoms.

Cholinesterase inhibitors prevent the breakdown of acetylcholine, a brain chemical believed to be important for memory and thinking. As Alzheimer's progresses, the brain produces less acetylcholineand, over time, these medicines lose their effectiveness. Because cholinesterase inhibitors work in a similar way, switching from one to another may not produce significantly different results, but a personliving with Alzheimer's may respond better to one drug versus another.

Lecanemab:

It is an FDA-approved immunotherapy to treat early Alzheimer's. It targets the protein beta-amyloid to help reduce amyloid plaques, one of the hallmark brain changes in Alzheimer's.

Clinical studies to determine the effectiveness of were conducted only in people with early-stage Alzheimer's, or mild cognitive impairment due to the disease.

Study results showed lecanemab slowed the rate of cognitive decline among study participants over the course of 18 months and reduced the levels of amyloid in the brain. Currently, insurance may onlycover this medication in specific situations.

Before prescribing this medication, doctors may order PET scans or an analysis of cerebrospinal fluidto evaluate whether amyloid deposits are present in the brain.

Possible side effects of this medication include brain swelling and bleeding. In rare instances, the sideeffects may be serious or life-threatening. Due to this potential risk, monitoring with routine MRIs is required.

Several other medications to treat Alzheimer's are being tested in people with mild cognitiveimpairment or early Alzheimer's[11].

Medications for moderate to severe Alzheimer's disease:

A medication known as memantine, an N-methyl-D-aspartate (NMDA) antagonist, can be prescribedfor moderate to severe Alzheimer's.

This drug is prescribed to decrease symptoms, which could enable some people to maintain certain daily functions a little longer than they would without the medication.

For example, memantine may help a person in the later stages of the disease maintain their ability to use the bathroom independently for several more months, a benefit for both people with Alzheimer's and their caregivers.

Memantine:

NMDA antagonist*:*

➢ Treats symptoms of moderate to severe Alzheimer's by blocking the toxic effects associatedwith excess glutamate and regulates glutamate activation.

➢ Possible side effects include dizziness, headache, diarrhoea, constipation, and confusion.Delivered once or twice a day through a tablet, liquid, or an extended-release capsule[14].

Brexpiprazole:

Atypical antipsychotic*:*

Treats agitation resulting from Alzheimer's. Possible side effects include common cold symptoms, dizziness, high blood sugar, and stroke. Delivered once a day through a tablet.

Donepezil:

Cholinesterase inhibitor*:*

- Treats symptoms of mild, moderate, and severe Alzheimer's by preventing the breakdown ofacetylcholine in the brain.
- Possible side effects include nausea, vomiting, diarrhoea, insomnia, muscle cramps, fatigue,and weight loss.
- Delivered once a day through a tablet.

II. SCREENING METHODS FOR AD

A.BIOMARKERS:

Accumulating data has focused on discovering, evaluating, and validating biomarkers for applicationin clinical research.

Biomarkers are employed to confirm and improve on diagnostic accuracy of dementia. In AD, biomarker development and validation has focused primarily on cerebrospinal fluid (CSF) -omics, including proteomics, and PET ligands to detect CNS amyloid beta (Aβ) or tau/tangles the two pathological hallmarks of AD.

Biomarker discovery and validation include collection methods, processing procedures, sample storage, and assay standardization within and across laboratories.

In response to these criticisms and concerns, an international working group (Alzheimer's Precision Medicine Initiative) was formed to review the current state-of-art for blood- based AD biomarkers.

These would be preferable given that blood tests are more feasible in world-wide settings, are less costly (compared to PET) and less invasive (compared to lumbar puncture for CSF collection).

To date, 19 blood-based biomarkers were selected by the working group for additional consideration for AD detection. This working group also outlined a pathway from biomarker identification and development to validation so that academic-industrial partnerships in cooperation with regulatory bodies may co-develop putative blood-based AD biomarkers.

Validation of biomarkers should start with assessment in a "black and white" panel study. Samples from patients with a diagnosis of AD would be compared to samples in neurologically healthy controls.This "black and white" study would aim to establish a concordance between the novel biomarker andthe standard measure. This would be an attempt to validate the overall accuracy of the biomarker in aknown group design.

The next step is attempting to replicate the results in a set that more accurately reflects primary care. This second study would implement the technology from the developing laboratory and would involvetechnology transfer to an existing diagnostic assay that is widely available.

The next step is refining the diagnostic algorithm, which would allow a case for potential regulatory approval. Finally, to establish interlaboratory replication, samples would be assayed on the intended equipment for regulatory approval.

An optional step is the validation using CSF samples obtained from the same patients in the first study.

Big data initiatives based on -omics data (Big Data Research and Development Initiative) analyses large multidimensional blood-based omics data—allowing stratification of populations into well- defined subgroups (sharing commonalties) that may accelerate progress in biomarker development[28].

B. NEUROIMAGING:

A variety of neuroimaging modalities have been developed with the goal of detecting dementia earlieralong the AD spectrum and discriminating among the dementia differential diagnosis.

The Alzheimer's Disease Neuroimaging Initiative (ADNI) connects researchers across the US and Canada to collect, validate, and use pooled data (and samples), including MRI and PET neuroimaging,genetic data (genome-wide association study or GWAS), cognitive testing, CSF -omics, and blood- based biomarkers. Although the leading neuroimaging methods are PET and MRI, other modalities are employed such as computed tomography (CT).

Although CT is considered less sensitive than MRI for studies in dementia, CT is particularly useful for detecting bone lesions and new haemorrhage. Other advantages of CT over MRI include lower cost, shorter acquisition time, and no contraindication with claustrophobia or implanted metallic devices such as a pacemaker.

SPECT, a nuclear imaging technique integrating CT and radioactive tracers, is also used in dementia diagnosis including, for example, differentiation of FTD from Jakob-Creutzfeldt Disease (JCD).

Functional MRI (fMRI) is a non-invasive technique that measures brain activity indirectly via changes in blood oxygenation. Functional MRI is useful in assessing integrity of brain networks in prodromalstages of AD, thus detecting mild cognitive impairment (MCI)and in discriminating LBD from AD[29].

C.ELECTROENCEPHALOGRAPHY:

Electroencephalographic (EEG) recordings have also been assessed for diagnosing dementia. EEG records electrical activity of cortical neurons and thus indirectly represents underlying brain function.

EEG recording abnormalities are found in subcortical dementias, for instance, in DLB and PDD. Similar to other methods, the goal is to achieve earlier diagnosis with EEG, which is also a non- invasive technique.

However, unlike PET or MRI scanning, EEG recordings are comparatively inexpensive and widely available at clinical centers. EEG methods are sometimes divided into two approaches.

The first is accomplished in the resting state (awake at rest) in the absence of any stimulus. Since thepatient is not required to perform a behavioural task, it is more comfortable and less stressful for patients.

There are four effects of AD that have been reported in repeated studies in resting state EEG. There isa slowing of the power spectrum from high frequency (alpha, beta, gamma) to a low frequency in patients with AD.

The shift from higher frequency to lower frequency is proportional to the progression of AD. There isa reduction of EEG signal complexity in patients with AD, which is likely caused by neuronal death.

Decreased in synchronization is observed in patients with AD, which is a result of decreasedconnectivity between brain areas.

The cause of desynchronization is not well understood, it may emerge from atrophy of neural networks.

There are neuromodulatory deficits in AD patients with their cross-frequency interaction. For example, beta rhythms modulated at a theta rate is more pronounced in controls than in AD patients[30].

D.ELECTROVESTIBULOGRAPHY:

Electrovestibulography (EVestG) is a vestibular-based diagnostic test that measures field potential activity recorded in the external ear canal in response to vestibular stimuli.

The EVestG test is very similar to electrocochleography, but with the acoustic input replaced by a series of mechanically-driven orthogonal tilts accomplished by having the subject sit in a tilt chair (tiltsin 2 dimensions—left/right and forward/backward).

Recordings are made when the chair is static and also while moving. To date, EVestG methodology has been applied toward diagnosis and discrimination of PDD (Dastgheib et al. Med Biol Eng Comp,in press) vs. other neurological disorders, such as schizophrenia, depression, and Meniere's Disease.

Overall, sensitivities and specificities have been typically above 85%. EVestG is more than 95% accurate in PDD diagnosis in patients that were at different stages of the disease.

EVestG may provide a quick and non-invasive screening tool for PDD. Given the accuracy of PPD and PDD diagnosis, future research using EVestG should be conducted in other neurodegenerative disorders.[31].

E.OLFACTION AND TASTE:

Humans are capable of growing new nerve cells throughout life in a process called neurogenesis suggesting a novel treatment srategy for dementia.

To date, the two human brain regions that are sites of adult neurogenesis are a subfield of the hippocampus and the olfactory bulb[32].

In fact, olfactory disorders may predict pre-dementia and dementia. Given this, it was hypothesized that olfaction and neurogenesis may be impaired in those with dementia, and that olfactory disorders may predict the conversion from MCI to AD dementia.

Presently, no gold standard olfactory test is available for diagnosing or monitoring AD in clinical practice, but efforts have been made for predicting AD and for discriminating dementia diagnoses.

For example, Williams etc, found that that olfactory impairment was more pronounced in patients with mild DLB than in those with mild AD[33].

Interestingly, in another study patients with AD may demonstrate an asymmetrical decrement of odourdetection sensitivity (left worse than right). In this study, the left-right nostril odour detection test functioned as an inexpensive, sensitive and specific test for probable AD[34].

F. VISION:

Vision is impaired in dementia—with a variety of demonstrable impairment including contrastsensitivity. More recent studies examined whether a retinal examination may predict AD earlier and reveal disease progression. Mahajan et al., found ocular changes in AD besides decreased contrast sensitivity and included decreased vision, abnormal pupillary reaction, visual field changes, loss of retinal ganglion cells (and retinal nerve fiber layer), peripapillary atrophy, increased cup– disc ratio, retinal thinning, tortuosity of blood vessels, and the deposition of Aβ in the retina[35].

G. SALIVA:

Using saliva samples to diagnose AD has several advantages such as the non-invasive ease of acquisition and low cost.

Used saliva and immunoblot analysis to quantify the phosphorylated tau (p-tau)/total tau (t-tau) ratioat different phosphorylation sites[36].

Hyperphosphorylated tau (indicated by p-tau) is a pathological marker for AD. In this study, sampleswere obtained from AD, MCI,

and FTD patients. With one phosphorylation site, Ser-396, the p-tau/t-tau ratio was significantly increased in patients with AD compared with elderly control subjects. However, the sensitivity and specificity were not sufficiently robust to serve as a standard clinical biomarker.

In fact, about one third of the AD group failed to show elevations of salivary tau. Another study withsaliva measured salivary acetylcholinesterase (AChE) activity in AD—an enzyme deficient in AD patients[37].

The study examined in 15 AD patients who were taking memantine vs. 15 healthy subjects. AChE activity in saliva in the AD group was indeed lower compared to the control group, but there was no significant difference between groups.

H. SPEECH:

Speech impairment is well-known in AD and other dementias and impairment in verbal communication depends on AD stage. Progression of speech impairments vary by individual, but threestages are identified[38].

In the first, subjects demonstrate word-finding difficulties. In the intermediate stage, vocabulary and language become weaker. In the advanced stage, subjects provide only limited answers consisting of a few words. Nasrolahzadeh et al, examined speech in AD subjects with the goal of utilizing spontaneous speech for earlier detection.

This study focused on analyzing and comparing the quadratic phase coupling of spontaneous speech signals from healthy controls (n = 30) vs. AD subjects (n = 60) using bi-spectrum and bi-coherence methods. Signal processing methods of this type are statistical methods utilizing non-linear interactionsof a continuous spectrum of propagating waves in one dimension[39].

All participants were asked to tell “graceful personal stories, express their feelings, and converse in afriendly way.”

The results showed that the spontaneous speech signal of those with AD was significantly reduced compared to healthy controls.

In another study, speech samples were compared in probable AD subjects (n = 225) vs. probable DLB(n = 67) subjects[40].

In particular, speech samples were evaluated using the Cognitive Status Examination [COGNISTAT;formerly the Neurobehavioral Cognitive Status Examination (NCSE)], in which exam takers discuss what is happening between two people in a presented picture; however, other domains in addition to language may be tested, such as constructional ability, memory, calculation skills, and executive skills.During this test, subjects were scored (in a team effort by several psychologists) based on whether the subjects described or did not describe the relationship between two people during the speech sample. For instance, an example of the description group was as follows;

“This is a picture of fishing. Someone is calling over. The person fishing does not notice a fish caughton the hook because he dozed off.” In the no-description group, a typical answer may be “A person isfishing. A person is performing acrobatics on the bridge.”[41].

In addition, study participants were tested with the Mini-Mental State Examination (MMSE). The results suggest that patients with more severe overall cognitive dysfunction and also male patients areless likely to describe the relationship between two people.

Difficulties with picture naming tasks are one of the most frequently reported speech impairments in people with AD.

Verbal fluency tests are one of the most widely used measures of speech function in patients with dementia. These tasks assess the person's ability to retrieve and produce words relevant for the specifictask.

Letter fluency records the generation of as many words as possible beginning with a given letter, for example words that begin with the letter S.

Category fluency involves the generation of as many words as possible that fall into a specific category, for example tools.

Letter and category fluency place demand on executive functioning since patients must engage in verbal retrieval and recall and

inhibit incorrect responses.

A meta-analysis of 153 studies with 15,990 AD patients found that AD patients had impaired letter fluency.

Category fluency declines with the progression of AD. Naming difficulty is another well-documentedsymptom of AD and it typically occurs early in disease onset.

The Boston Naming Test (BNT) is a widely used test that comprises 60-items ranging from frequent to infrequent items. The patient is presented with an item and allowed approximately 20 s to verballyidentify the item[42].

However, some patients with dementia find the 60-item version difficult to complete due to their limited attention. Therefore, the BNT developed two 30-item versions that significantly correlated to each version and the 60-item version.

Differences have been found between patients with MCI and controls, and between AD and non-ADindividual A speech language pathologist can modestly improve communication for people with moderate to severe dementia[43].

Speech language therapy may offer some protection against further speech decline[44].

However, future studies should examine this question by measuring speech over a long period of time.Also, caregivers can be trained on the methods used by a speech language pathologist, which would lessen the time the patient must to be in the clinical setting[45].

I. NEUROPSYCHOLOGIC TESTING:

Detailed comparator studies as well as comprehensive reviews addressing tests used for assessing cognitive status in AD and other dementias are published[46].

Neuropsychologic tests may be organized by cognitive, functional, or behavioural domains (or their combinations) including activities of daily living (ADLQ), short mental status tests (MMSE, MoCA), brief dementia batteries (RBANS), behavioural symptoms (NPI-Q), clinical ratings (CDR), mood (Beck Depression Inventory II), IQ (Wechsler), executive function (Stroop test), visuoperceptual (drawing a clock), language or calculation (BDAE), and episodic memory (paragraph recall, word-listlearning, Rey-Osterreith Complex Figure). When administered as a battery, neuropsychologicalassessments quantify cognitive impairments and rates of progression[47].

The CANTAB is a touchscreen computer automated neuropsychological test battery, which measureslearning and memory[48].

Patients with AD are impaired on the CANTAB test battery as compared to controls. Virtual reality is used to measure spatial navigation, which is impaired in people with dementia[49].

The CANTAB and virtual reality could be integrated into family practice such that any medical professional could administer the task[50].

CONCLUSION:

Sustained increases in the prevalence of AD surely grab the attention of disease control authorities. Asthe disease prevalence is increasing in india day by day. More research need to be emerged in this field. AD is the most common neurodegenerative disease, and it contributes to the mortality rates in aged populations. So new therapeutics and treatment modalities are required, considering the progressive challenges posed by neurological diseases. Although numerous investigations have proposed new disease-modifying drugs, a lack of precise remedies for the treatment ofneurodegenerative diseases remains. Most treatment strategies focus on justifying AD symptoms as opposed to targeting pathophysiological factors. However, a limited number of target-acting moieties, gene therapies, and nerve regeneration therapies target the causative factors for removal. In addition, Aβ and tau immunotherapies for AD unite two complex biological mechanisms: the immune system and the nervous system. The recent FDA approval of aducanumab (an anti-Aβ monoclonal antibody) and lecanaumab for AD treatment has provided hope that new drugs that can fundamentally cure ADand other neurodegenerative diseases will be produced. Still further studies and research need to be carried

out to develop a potential therapeutic agents. Novel Screening methods must to be developed to reduce the progression of the disease condition.

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How to cite this article:
Kondumahanti V. N. Lakshmi et al. Ijppr.Human, 2025; Vol. 31 (4): 118-131.
Conflict of Interest Statement: All authors have nothing else to disclose.

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