Behavior patterns of Alzheimer's Patient- A better insight

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ABSTRACT: - Alzheimer's disease, also known as AD, is the most prevalent type of dementia, affecting about 35 million individuals globally and tending to get worse. There is a lack of effective medicines and preventative measures. But since the deadly progressive neurodegenerative illness was originally described in 1907, significant discoveries on the molecular pathways have been published. Research has documented the connections among cognitive performance, caregiver load, behavioral and psychosocial symptoms of dementia (BPSD) i.e., behavioral, and psychological symptom of dementia, and treatment outcomes. Nevertheless, it is currently unknown how caregiver burden and BPSD in community-dwelling Alzheimer's disease (AD) patients are related. This review article will examine the pathophysiology of Alzheimer's disease, as well as the behavioral patterns of individuals with the disease and its associations with other illnesses. This review article also examines the various cases and the effects of COVID-19 on individuals suffering from Alzheimer's disease. This review intends to raise awareness of potentially significant aspects of digital health, clinical outcomes, policy framework, and basic science. It also offers the research community recommendations for future studies and possible challenges related to leveraging gender and sex differences in the field of basic science. When examining new ideas about health, illness, pre-disease, and risk, Alzheimer's disease (AD) offers a valuable case study. A summary of disease biomarkers and drug targets is also given, and network biology techniques are recommended as fresh methods for finding novel biomarkers and medications.

KEYWORDS: - Alzheimer's disease, Neurology, BPDS, Sex difference, gender, Alzheimer's disease caregiver, AD, cerebral, Psychology, Future prospectus.

I. INTRODUCTION:

Alzheimer's disease is a devastating neurological condition that affects the brain predominantly and progresses over time. It causes cognitive decline, memory loss, and serious deficits in everyday functioning. It is the leading contributor of dementia in other adults and a significant worldwide health issue. < 10% of Alzheimer's patients have early arrival, which is rare and occurs before the age of 65. Alzheimer does not currently have a known cure.

AD is currently viewed as a model of complex neurodegenerative illness. In fact, several factors, such as the development of amyloid deposits, vascular abnormalities, and changes to the cerebrospinal fluid (CSF), may be involved in its pathophysiology. The combination of all thesefactors results in a state of hypoperfusion and inflammation that leads to weakness in the brain, excessive amyloid buildup, and ultimately an imbalance with neural networks.

Symptoms of Alzheimer's disease: -
• pre-symptomatic,
• mild, and
• Depending on the severity of cognitive impairment, Alzheimer's disease stage.

According to the Diagnostic and statical manual of Mental disorder-5 categorization of Alzheimer's disease, there are various steps. Amnesia with somewhat sparing long-term memory is the earliest symptom as well as can be triggered in many patients even if it isn't the presenting symptom. There is a decline in executive functioning, motivation, problem-solving skills, and organisation after amnesia, which makes it challenging to multitask and think abstractly. In the early phases, executive functioning impairment can range from modest to severe. In the medium to late stages, neuropsychiatric symptoms such apathy, social isolation, disinhibition, anxiety, unease, psychosis, and wandering is also frequent. Dyspraxia, olfactory dysfunction, sleep difficulties,

extrapyramidal motor indications such dystonia and akathisia, and symptoms resembling Parkinson's disease occur. [1,2,3]

II.   BACKGROUND:

German scientist Dr. Alois Alzheimer initially described Alzheimer's disease in 1907. It was described as a "neurodegenerative disease" by him. It was characterized by cognitive ability and serious behavioural abnormalities like restlessness, disorientation, depression, and anxiety. [4]

The most severe type of dementia is Alzheimer disease. As of right now, 50 million individuals worldwide suffer from this illness; if a treatment or preventative is not found, that figure will rise sharply to a total of 152 million by the end of 2050. [5]

Additional data about Alzheimer's disease and its effects on patients, their family, and the entire healthcare system includes the following:

- AD is the 6th disease which cause most of mortality in in the US as well as worldwide.
- Elderly people with Alzheimer's disease account for one in three deaths.
- According to a survey, 18.4 billion hours of care without pay are expected to be provided by more than 16.1 million carers.
- In every 65 second, a case of Alzheimer's disease is found. [6]

Epidemiologyof Alzheimer:

Globally, there will be 152 million people with dementia by the end of the century, with low- and middle-income countries expected to have the largest increase. [7] Acc. to facts and from 2020 about Alzheimer's disease, the number of AD sufferers (under 65 years old) could significantly rise from 5.8 million to 13.8 million in America and globally by 2050.[8] Community-dwelling investigations in China and Japan over the past few decades have shown a clearly rising AD prevalence.[9,10] Specifically, women had a greater age-standardized death rate than men, and their age-specific global prevalence was 1.17 times higher than that of men, suggesting that women's longer life expectancies were not the only factors leading to their dominance.[11] Furthermore, the number of mortality from AD increased by 146.2% between 2000 and 2018, placing it seventh above all causes that cause mortality among the elderly. It should be noted that carers will encounter increased mental strains and damaging emotional impacts. [8] Caregiving for the AD population will therefore place a heavy and unsustainable load on society

and families. The primary goal of much AD care is wellbeing. Patients with AD might experience puzzling issues and symptoms across numerous domains. Additionally, certain epidemiological studies have offered solid proof that environmental and behavioral factors are crucial in the pathophysiology and development of disease. Preexisting disease is more prevalent in AD patients than in others of a similar age, therefore maintaining physical health is crucial to safeguard cognitive. In addition, several risk variables might operate as both AD symptoms and contributors to the disease at the same time, according to the theory of reverse causality. Therefore, it is crucial for people with cognitive dysfunction to receive an appropriate diagnosis. Pre-symptomatic diagnosis is more difficult because some cognitively normal individuals with only the A and tau biomarkers never develop AD, despite these biomarkers being diagnostic of AD. [12]

Need of studying behavior patterns of Alzheimer disease patient:

Most research on dementia has focused on linguistic and cognitive losses, but more recently, alterations in personality and behavior have been noted. [13,14] On the other hand, attentional, executive, and semantic deficits are signs of the early stages of Alzheimer's disease, which is typified by abnormalities in antegrade episodic memory. [15] Ritualistic and conventional actions are among the numerous clinical characteristics of fvFTD that have been discussed in the literature. These include basic behavior (such as grunting, tapping one's foot, or grunting), dressing or toileting rituals, wandering and pacing along an established route, continuous reactions, and the use of cliched language [16]; superstitious rituals [17], cleaning in excess, and drinking specific drinks in a particular order. [18]

The prevalence of stereotypical behavior is higher overall in FTD than in Alzheimer's disease, according to a few recent studies that have started to examine this behavior in greater detail. These studies have also suggested that the presence of such features may have the ability to discriminate between FTD and Alzheimer's disease. [14,19,20]

These investigations have shown that individuals with FTD exhibit stereotypical actions frequently, however some issues remain unanswered. Are there any differences between people with fvFTD and semantic dementia other than the quantity, rather than the quality, of

stereotypical behavior? Do people with Alzheimer's disease later exhibit this behavior? What, if any, connection exists between these behavioral signs and cognitive impairment?

Gender specification: -
According to studies, women are more likely than men to develop Alzheimer's disease. [21] Given that ageing is one of the major risk factors for developing Alzheimer's disease, the higher female frequency has frequently been connected to men's shorter life expectancy than women [22,23]. However, mounting evidence suggests that this is not just one aspect at play; biological & socio-cultural systems may be also involved.

Alzheimer's disease clinical outcomes and sex and gender inequalities: -
There are a few disparities between men and women with AD in terms of their clinical characteristics. In various reviews, we have outlined these distinctions [24,25,26]; a special issue with a focus [27], moreover in the several textbooks on the subject. [28,29] In result, the body of evidence points to the importance of sex in the phenotypic variability of AD and cautions against ignoring it in preclinical or clinical studies. To produce solid enough data to inform clinical practice and policy, the analysis and reporting of gender disparities in clinical investigations must be greatly enhanced. [24,30,31] It's interesting to point out that the evidence suggests considerable gender and sex disparities along the AD continuum, which vary depending on the disease stage.

During the prodromal stages, women appear to be more protected than men; curiously, women exhibit better cognitive performance for a given level of hippocampal neurodegeneration. [32] In collaboration with the Alzheimer's Precision Medicine Initiative, we have found sex variations in the AD biomarker of amyloidosis, degeneration of the brain and rsFC in mentally healthy individuals older than 70 years of age" (APMI). Particularly, the anterior cingulate cortex of men accumulates more in vivo brain amyloid load than that of women. This suggests that a higher amyloid load is required before symptoms in men appear. [33] Women exhibit greater behavioral and executive reserve than men in the behavioral variant of frontotemporal dementia (bvFTS), and neurodegeneration in women must be more severe to produce symptoms like those in men. [34]

Women with mild cognitive impairment (MCI) advance twice as quickly as men do after clinical diagnosis, in contrast to the menstrual products shown in the early stages. [35] A result that might have effects on how patients are managed and how clinical trial designs are approached. According to a very intriguing line of research, women who are in the early stages of AD may not receive a diagnosis based on conventional neuropsychological tests. These tests tend to be too simple for women because they perform verbal memory better than men, missing the start of the diseased process. Since women are further along in the progression of the illness than males, they would be detected at later stages, which could explain the rapid decrease observed after diagnosis. [36] A number of biomarkers, like as imaging, fluid, and electronic ones, have been created for AD and are currently being employed more frequently in research and therapeutic contexts. Such biomarkers may have different diagnostic and prognostic significance for men and women, even in the preclinical phases (WBP, publication in progress). The WBP is pushing for the implementation of a new, AI-powered biomarker-based clinical framework in conjunction with the APMI and cohort program (APMICP) to close the gender gap. [37]

There may be differences between males and women's risk factors for Alzheimer's disease. There is increasing proof that APOE4(a strongest risk factor gene for Alzheimer's disease) susceptibility is sex-specific [38,39,40], moreover it has been noted that sex-genotype interactions affect how people respond to cholinesterase inhibitors and hormone replacement therapy. [41,42,43] In addition, midlife cardiovascular risk factors are associated with a higher risk of dementia in women than in males. [44] It is generally established that lifestyle-related risk factors might affect AD risk (by as much as 40%) in addition to hereditary factors [45], Since disparities are linked to both gender and biological sex, it is crucial to emphasize that many of these modifiable hazards are known to occur differentially across sexes and genders. [25]

The likelihood of developing AD might vary depending on a person's psychological state, level of social involvement, pre-existing diseases like diabetes and brain injury (TBI), or their lifestyle habits. For instance, numerous studies have shown a link between diabetes and Alzheimer disease. [46,47,48] Furthermore, a study that looked at different levels of injury and their effect on Alzheimer disease described a favourable link between TBI and Alzheimer disease. [49]

The emergence of highly diverse patient subgroups with distinct illness trajectories, unique risk factors, and likely unique neurobiology, like the situation in oncology, would require a new approach where the generated data can be multiplied in a combinatorial manner with medical, biomarker, and other omics data to produce methods for the estimation, evaluation, prognosis, and treatment of Alzheimer disease. [50]

These statistics suggested that female patients would face difficulties to participating in clinical trials because they make up much to 65% of the actual population of people with AD. Some of them may be brought on by standards that routinely exclude women, like a lower degree of education. [51]

Brief introduction about Alzheimer disease: -
Dementia of the most frequent type is Alzheimer's disease (AD). It is now widely accepted that the disease progresses through a few stages before developing into full-blown dementia. Amyloid plaques, which are made of aggregated beta-amyloid (A) protein, begin to build up in AD patients' brains up to 20 years before symptoms appear. [52,53] One of the approximately 40 amyloidosis that have been described, Alzheimer disease is characterized by the abnormal deposition of endogenous, typically soluble proteins as amyloid fibrils in numerous organs. These illnesses, which include Parkinson's disease, the prion diseases, type II diabetes, Huntington's disease, and amyotrophic lateral sclerosis, or AMD, each entail a distinct protein and clinical profile. [54] There are currently 46.8 million cases of dementia worldwide, and by the year 2050, there will likely be over 131.5 million cases. The cost of dementia-related medical treatment exceeded $818 billion (USD) in 2015, and it is predicted that this amount could reach $2 trillion by 2030. [55] Although the greatest established risk factor for AD is old age, some people may experience the onset of AD at a younger age. Consequently, AD is divided into two types based on the timing of onset. [56] Late-onset AD (LOAD), which commonly affects those over 65, and early onset AD (EOAD), which typically occurs before that age. Rare, dominantly inherited mutations in APP, PSEN1, and PSEN2 are the root cause of EOADIrregular AD, another name for LOAD, is a disorder with a high genetic component. As much as 60–80% of LOAD is inherited, even though environmental and genetic factors play a significant role in the onset, progression, and severity of the illness. [57]

In 1907, the very first Alzheimer disease episode was described. Since then, significant advancements and discoveries have marked the history of Alzheimer's disease research in the broader context of illnesses linked to amyloid. Virchow used the name "amyloid" in 1854 to characterise the macroscopic irregularities connected to clinical symptoms that, when stained with iodine, appeared to indicate the amylaceous components of plants. [58]

Staging: -
a. **Preclinical or Pre-symptomatic: -**Individuals have the appropriate laboratory evidence but are asymptomatic at this point. At this point, Alzheimer disease diagnosis can be aided by identifying the biochemical signs. Although they are not exclusive to Alzheimer's disease, low levels of amyloid and elevated tau proteins in CSF function as biological indicators.

b. **Mild Cognitive Impairment: -** Patients have deterioration in non-memory domains like language function or executive abilities at this point. These people are still working, interacting with others, and carrying out autonomous tasks. 10% of patients with mild cognitive impairment develop dementia annually. The degree of impairment at the time of diagnosis is one of the risk factors for dementia progression in addition to the other risk factors for dementia.

c. **Dementia: -**Patients suffer severe memory impairment at this point. A decrease in natural verbal output, phenomics' paraphrastic errors, anomia aphasia, and a propensity for the circumlocution to avoid lost words are examples of language abnormalities. Aristogenesis, or constructional incapacity, and meandering through familiar environments are caused by impairments in visuospatial abilities.

Common symptoms: -
The following are the most typical signs and symptoms of Alzheimer disease: [59,60]
1. **Decreased capacity to absorb and retain new information:**
The most common symptoms of Alzheimer disease are cognitive abnormalities, such as neglecting recently learned material, missing important dates or occasions, repeatedly asking the same question, and increasingly depending on memory aides.

2. Difficulties with complex tasks and reasoning:

A few individuals notice changes in their capacity to plan or work with numbers. It could be difficult for them to follow a natural recipe and keep track of daily spending. They can experience concentrate problems and take longer to finish the work than they did earlier.

3. Difficulty in carrying out routine duties:

Individuals suffering from Alzheimer's disease often believe that carrying out daily tasks is challenging. People occasionally could experience difficulties navigating a familiar area or handling a financial constraint at work.

4. Losing stuff and failing to remember how to go back a step:

Patients with Alzheimer disease may forget objects they put in unexpected places. When that happens, they are unable to resume their search for them. They frequently begin blaming others for losing them. It could occur occasionally after some time.

5. Difficulty in speaking, reading, and writing:

It may be challenging for people with Alzheimer disease to follow along in a conversation or take part in it. They might halt a conversation and be unsure of how to resume it, or they might begin to recount the events. They could struggle to use proper language, struggle with jargon, or refer to things incorrectly.

6. Personality and mood changes:

People with Alzheimer disease may develop new personalities and mindsets as they grow increasingly perplexed, nervous, agitated, frightened, or suspicious. At work, at home, among friends, or in other situations where they are uncomfortable, they could become irritated.

7. Reduced spatial awareness:

Some AD patients may experience vision issues. They might have trouble judging distances and complexity of colours, which could be problematic while driving.

8. Time or location uncertainty:

Patients with Alzheimer disease may have trouble keeping track of the seasons, dates, and times.

Although the rate at which the disease progresses differ from person to person, AD symptoms get worse over time. It is separated into seven stages based on how a person's capacity changes after experiencing symptoms brought on by cognitive functioning deficits in Alzheimer disease. [60]

1: No Cognitive Impairment
2: Very Mild Cognitive Impairment
3: Mild Cognitive Impairment
4: Moderate Cognitive Impairment
5: Moderately Severe Cognitive Impairment
6: Severe Cognitive Impairment
7: Very Severe Cognitive Impairment

Pathophysiology: -

Alzheimer's disease is characterised by abnormal neurotic plaque accumulation and neuronal tangles.

Plaques are tiny, circular lesions with an external amyloid beta-peptide core and an expanding axonal end. The beta-amyloid peptide originates from a transmembrane protein called the amyloid protein precursor (APP). As proteases, alpha, beta, and gamma secretases cleave the beta-Amyloid peptide from APP, among others. APP is usually cleaved by alpha- or beta-secretase, and the tiny fragments that remain safe for neurons to ingest. Nevertheless, 42 amino acids in peptides (betaamyloid 42) are produced by the sequential cleavages of beta-secretase and gamma-secretase. An increase in beta-amyloid 42 levels result in the production of amyloid aggregates that cause harm to neurons. Collective fibrillary amyloid protein synthesis is preferred over usual APP degradation by beta amyloid 42. APP is located on chromosome 21, one of the chromosomal areas linked to Alzheimer's disease in families.

Amyloid builds up around the meningeal, intellectual, and grey matter arteries in Alzheimer's disease. Miliary formations known as plaques are consolidated deposits of multifocal grey matter. On the other hand, some individuals with dementia did not show any amyloid plaques at all during brain scans, while others with dementia did show plaques. Neurofibrillary tangles are fibrillary intracytoplasmic structures that are created in neurons by a protein called tau. The primary function of tau protein is to stabilise axonal microtubules. Microtubules are present along the axons of neurons and are required for intracellular trafficking. Microtubule assembly is held together by the tau protein. In Alzheimer's disease, tau is hyperphosphorylated and extracellular beta-amyloid aggregation causes tau to form tau clumps. The abnormal pairs of helical filaments composed of tau clumps are known as neurofibrillary tangles.

Before dispersing throughout the cerebral cortex, they first emerge in the hippocampus. Tau aggregates are accumulated inside the neurons. The

Braak staging, developed by Braak and Braak, is based on the geographical staging of neurofibrillary tangles into six stages and is included in the neuropathological criteria for the identification of Alzheimer disease used by the National Institute on Ageing and Reagan Institute. Tangles have a higher association with Alzheimer's disease than plaques do.

Another sign of Alzheimer's disease is granulovacuolar degeneration of hippocampal pyramidal cells due to amyloid angiopathy. Certain studies indicate that cognitive impairment is more strongly associated with a decrease in the density of presynaptic boutons from pyramidal neuron cells in laminae III and IV, as opposed to an increase in plaque density.

Low levels of acetylcholine have also been linked to neuronal loss in the Meyner Nucleus Basalis. The exact role of the vasculature in the degenerative process of dementia is unknown. Subcortical infarcts cause a four-fold increase in the risk of dementia. Cerebrovascular disease exacerbates extent and rate of dementia progression. [61,62,63]
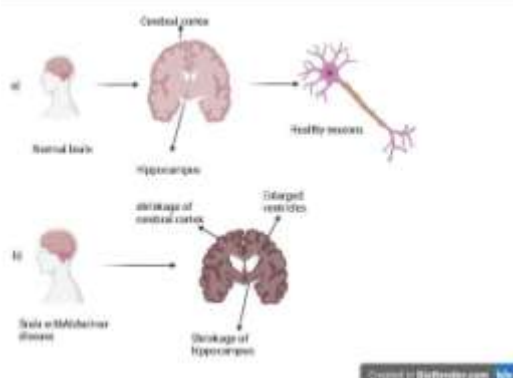

Figure1.1: - The physiology of neurons and the brain (a) healthy brain and (b) brain with

Alzheimer's disease.
Linkage of Alzheimer with other disorder: -
a. Linkage of Alzheimer with Parkinson disease: -

Both Parkinson's disease and Alzheimer's disease are neurodegenerative conditions that fall under the umbrella category of dementia. Many professionals refer to dementia as a syndrome rather than a particular disease due to the ambiguity of the dementia medical classification. These neurological conditions are frequently misdiagnosed as dementia due to their similarities, but Alzheimer's and Parkinson's have different symptoms, prognoses, and therapies. While both Parkinson's and Alzheimer's are progressive neurological disorders, Parkinson's disease has a greater impact on physical function than Alzheimer's patients have on their ability to think clearly.

Parkinson's disease is a neurological condition that develops as brain neurons deteriorate or die. Movement is impacted by a breakdown in communication that occurs when nerve cells get sick and are unable to engage with other cells adequately. Tremors (uncontrollable shaking or shuddering) in the arms, hands, head, jaw, or legs are common symptoms, as are stiff limbs, delayed mobility, and poor balance or coordination. Parkinson's disease symptoms progress similarly to those of Alzheimer's disease over time, becoming more pronounced.

Parkinson's disease is often found in elderly persons, just as Alzheimer's. Parkinson's disease is typically diagnosed at roughly age 60, and cases that appear before age 50 are referred to as earlyonset Parkinson's.

The primary signs of AD's neuropathological alterations include brain atrophy, an abundance of extracellular A plaques, and an accumulation of intraneuronal neurofibrillary tau tangles. [64,65] Patients with PD exhibit slow movements, tremors, abnormalities of the gait and balance, as well as other behavioural issues. [66] Lewy bodies, which are aberrant filaments consisting of -synuclein, and the gradual degradation of dopaminergic neurons that occur in the substantia nigra are the two principal pathogenic features of Parkinson's disease (PD). [67,68] Several clinical and pathological characteristics of the two neurodegenerative disorders are similar. The toxic effects of the tau, A42, and -synuclein proteins induce a variety of comparable cascades of neuronal events that result in progressive neurodegeneration in PD and AD patients. Oxidative stress, mitogen-activated protein kinases, cell cycle re-entry, glycogen synthase kinase-3 beta activation, and other crossover pathological changes. [69]

Apart from to the parallels among Alzheimer's disease and Parkinson's disease some possible pathways, including the Lewy pathology and -synuclein overexpression in AD, have recently been discovered. According to several investigations, Lewy bodies made up of additional -synuclein aggregation were present in up to 50% of AD patients. [70,71]

Neurodegenerative disorders and oxidative stress:

Cell respiration, metabolism, energy production, intracellular signalling, free radical production, and apoptosis are all influenced by mitochondrial function. Protease and phospholipase activation, decreased calcium buffering, limited energy production, and increased oxidative stress are all symptoms of mitochondrial dysfunction in neurodegenerative disorders. In these conditions, oxidative stress induced activation of microglial cells, protein aggregation, neuroinflammation, and mitochondrial dysfunction result in the death of neurons.

b. Linkage of Alzheimer disease with depression: -

Depression symptoms are widespread in AD and affect 20–30% of individuals. [72] About 300 million individuals worldwide suffer from depression, a significant medical disorder that can worsen pre-existing illnesses and increase functional incapacity. [72,73] Clinical data point to a connection between depression and AD. However, it is still not apparent if depression is a risk factor for Alzheimer's disease, a sign of neurodegeneration that manifests early, or a response to early cognitive abnormalities. [74,75]

According to several research, rather than coming before AD, depressive symptoms appear to appear right away after it. [76] Additionally, data from other studies show that depression only slightly affects dementia [77] & doesn't raise the chance of getting Alzheimer's disease [78]. However, according to other scientists, having depression worsens functional deterioration and raises the chance of behavioural issues in people with AD. [79] Revealed that among patients with AD, depression was the risk factor most consistently linked to behavioural. or psychological signs and cognitive deterioration. Additionally, several studies found a link between late-life depression and a higher risk of Alzheimer's disease, vascular dementia, and all types of dementia [80,81,82,] and it has been regularly proven that dementia risk is two times higher in late-life depressed individuals. [83,84]

Linkage of Alzheimer's disease with Type II diabetes: -

Alzheimer's disease (AD) and type 2 diabetes (T2D) are both prevalent in ageing populations, and T2D has been identified as a significant risk factor for AD. Both disorders are thought to have a heritability of more than 50%.

Alzheimer's disease (AD) and type 2 diabetes (T2D) commonly co-occur in older persons and are affecting an increasing number of people. Alzheimer's disease (AD) is a long-term neurodegenerative condition of the central nervous system that causes gradual memory loss, cognitive impairment, and behavioural abnormalities. The World Alzheimer Report predicts that from 10.5 million patients today, there would be 18.6 million by the year 2050. [85] A tight connection between T2D and AD has been revealed by recent epidemiological studies. According to a cross-sectional study, those with T2D who are between the ages of 45 and 65 are more likely to experience cognitive dysfunctions. [86] Another cross-sectional investigation among older Chinese people with T2D also revealed a connection between T2D and dementia. [87] According to a five-year follow-up research, people with diabetes had a 65% higher risk of developing Alzheimer's disease than people without the condition. [88]

It has been suggested that systemic inflammation, insulin resistance, mitochondrial dysfunction, and oxidative stress are all part of the shared pathophysiology of AD and T2D. [89,90] It is widely recognised that insulin resistance is a major factor in the development of type 2 diabetes and has been strongly linked to memory loss. [91,92] Hence, AD was proposed to be the type 3 diabetes mellitus. [93]

It is commonly acknowledged that interactions between inherited and environmental factors have a role in the development of both AD and T2D. For T2D, heritability is predicted to be greater than 50% [94] and as well as 79% for Alzheimer's disease. [95]

Current treatment options used for the treatment of Alzheimer's patient: -

Given that dementia usually affects persons over 60, the lifespan is expanding, which is causing the number of dementia sufferers to rise quickly, [96] AD has sparked a rapid expansion of treatment-related research. However, despite all the laborious research efforts, there are currently no cures for the illness. [97,98]

The goal of all currently approved treatments for the condition is to balance the transmitters involved. These drugs (AChEIs) that have been approved for the treatment of AD include donepezil, galantamine, and rivastigmine. [98,99] Their creation was founded on the cholinergic hypothesis, which contends that memory, attention, learning, and other higher brain processes deteriorate in AD because of a steady decline of

limbic and neocortical cholinergic innervation. Moreover, neurofibrillary degeneration in this region is probably the origin of the extensive presynaptic acetylcholine denervation that follows cholinergic cell dysfunction and death in the basal forebrain. By raising the level of acetylcholine at synapses, the AChEIs are clinically demonstrated to be beneficial in delaying the cognitive decline linked to AD. [100]

Current Alzheimer's disease treatment includes: -
These days, efforts are focused on managing AD holistically, particularly based on the following components:

1. Open conversation between the doctor and patient, the carer, and the person will allow for the accurate identification of symptoms, accurate evaluation and assessment, and appropriate counselling.

2. **Behavioral techniques**:
- Environment uniformity and simplification. [101]
- regular practices. [101]
- Communication techniques include remaining calm, offering enjoyable activities, using straightforward language, and only "saying no" when safety is at risk. [101]
- Planning for upcoming legal and medical requirements and decisions. [101]
- Cognitive behavioural therapy [102,103];
- Music treatment, light therapy, and exercise therapy. [102,103]

3. Carer assistance:
- brief relaxation breaks for the carer are scheduled.
- Psychoeducation entails recognising the cognitive, functional, and behavioural effects of dementia, establishing reasonable expectations, and avoiding situations that could aggravate symptoms or put one's safety and well-being at danger.
- promoting the establishment of carer support networks. [101]

Medicines for Alzheimer's authorized by the FDA: -
The only Alzheimer's disease treatments recognized by the FDA are the AChEIs donepezil, galantamine, rivastigmine, and the NMDA antagonist memantine. [101]
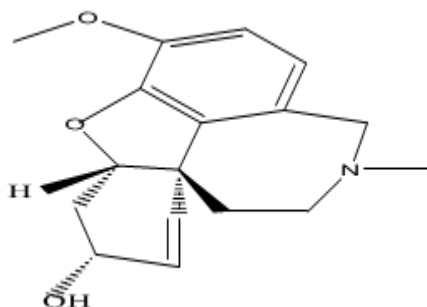
1. Donepezil: -
Donepezil is a cholinergic drug derived from piperidine that inhibits acetylcholinesterase, the enzyme responsible for breaking down acetylcholine, centrally, reversibly, and non-competitively. Additionally, donepezil influences the molecular and cellular aspects of AD pathogenesis by preventing certain glutamate-induced excitotoxicity-related consequences, lowering inflammatory cytokine expression early on, triggering a neuroprotective variant of AChE, and lessening the effects of oxidative stress. [104]

In 1996, it was approved for the pharmacological treatment of people with mild to moderate AD. Donepezil is administered orally as a pill, liquid, or jelly, as well as trans dermally. For mild to severe dementia, it is recommended to begin treatment with 5 mg/day and escalate to 10 mg/day for four to six weeks. The dosage may be increased to 23 mg/day if a patient with moderate to severe dementia has been taking the 10 mg/day dose for at least three months. [105] A 10 mg/day dose of donepezil has been demonstrated to enhance cognitive function, fundamental daily living skills, and clinician-rated overall impression ratings, but not behavior or quality of life. [106,107,108,109]

Additionally, studies on the efficacy of doses up to 23 mg/day have not revealed any appreciable variations from 10 mg/day dose. [110,111] However, none of the doses investigated has able to stop AD's development. [112] However, this medication is distinguished by strong patient compliance and little side effects, particularly when it comes to the brain or gastrointestinal systems. [113]

2. Galantamine: -
A selective, viable, and reversible acetylcholinesterase inhibitor, galantamine is a tertiary is quinoline alkaloid. Additionally, it enhances acetylcholine's natural ability to function on nicotinic receptors. [114] Oral administration is used with dosages of 4, 8, 12, 16, & 24 mg, administered twice daily as a quick-release solutions or once daily as an extended-release capsule. The recommended therapeutic dosage is 8 mg/day at first, increasing to 16 mg/day twice daily after 4– 8 weeks as a maintenance dose. [115]

Galantamine's capacity to work at the level of the nervous system's centre with limited activity in the periphery system makes it particularly intriguing in terms of its use in AD. In this vein, galantamine has been linked to many molecules that facilitate its distribution to the brain, including chitosan, solid lipid nanoparticles, and hydroxyapatite particles that contain cerium.[116,117,118] According to a recent meta-analysis by Li et al., this medication is the best option for treating AD because it not only works to control behavioral symptoms but also enhances cognitive function, daily living skills, and clinicians' assessments of patients' overall health.[119] Although this medication has demonstrated acceptable safety and tolerability, it is not without side effects, including convulsions, severe nausea, cramping in the stomach, vomiting, erratic breathing, disorientation, muscle weakness, and watery eyes.[120]

3. Rivastigmine: -

This medication, which was introduced in Switzerland in 1997 and received FDA approval in 2000, is recommended for the treatment of mild to moderate AD and mild to severe Parkinson's dementia. The mechanism of action of this pseudo irreversible inhibitor of butyrylcholinesterase and AChE is attachment to the anionic and stearic sites of AChE. [121] In case of adequate tolerability, the dose can be increased to 13.3 mg/day with initial dose of which 4.6 mg/day and available as transdermal patches. [122] Additionally, such method enables continued release for 24 hours, preventing digestive side effects brought on by intestinal and liver metabolism. Likewise, transdermal patches are an especially intriguing alternative for AD patients, who frequently experience memory loss and swallowing problems that make it challenging to use the oral route. [123] However, it must be mentioned that due to side effects such nausea,

vomiting, diarrhoea, loss of appetite, and stomach pain, patients using rivastigmine do not adhere to their treatment regimens very well. Additionally, a drug overdose may result in a few symptoms, including quick or sluggish breathing, chest pain, and a slow or irregular heartbeat. [124]

N-Methyl D-Aspartate (NMDA) Antagonists: -
• Memantine: -

It is a voltage-dependent, intermediate affinity, non-competitive NMDA receptor antagonist. High Glutamate tonic level pathologically prevents neuronal dysfunction. Both the manifestation of symptoms and the development of AD into neurodegenerative dementia are influenced by the dysfunction of glutamate-mediated neurotransmission, notably at the NMDA receptors. [125] it was the first authorised medication by the US FDA for treating Moderate to severe Alzheimer symptoms. [126])

On the other hand, the FDA has also approved memantine and donepezil combined therapy (Namzaric®) for the symptomatic management of moderate to severe Alzheimer's disease. However, the European Medicines Agency has not authorised Acescent®, a medication based on the hydrochlorides of memantine and donepezil, because there is insufficient evidence to support its efficacy in treating this pathology. [127,128] This combination of drugs prevents both the negative effects of excessive glutamate and the breakdown of acetylcholine in the brain. Memantine + donepezil is more effective than treatment or placebo at enhancing cognition as assessed by the ADAS-Cog and SIB scale, according to scientific research, overall evaluation, daily activities, and symptoms of neuropsychiatric disorders. [129]

Alternative therapies: -

1. **Physical exercise or activities: -** Prevention outcomes from adopting a healthy lifestyle that includes exercise, a Mediterranean diet, and sufficient sleep have been encouraging.
2. **Diet: -** The Mediterranean diet addresses the main risk factors for AD and protects cognitive function by offering a range of foods with oxidative and neuroprotective properties. Indeed, it has been found that following this type of dietary plan effectively reduces insulin resistance.
3. **Sleep patterns: -** As a result of an inflammatory process brought on by these sleep disturbances, and research has shown that sleep issues are positively correlated with

the aetiology of AD, exacerbating the behavioural, cognitive, and memory abnormalities associated with this illness.

Complementary Therapies: -
Care of behavioural symptoms and states of depression or anxiety, which are extremely typical clinical manifestations in patients with AD, has shown to be successful when using alternative healthcare through aromatherapy and music therapy in addition to the previously mentioned strategies. [130] The treatment for Alzheimer's disease also includes physical therapy, which uses cognitive and behavioural exercises to enhance patients' quality of life and, as a result, that of them carers. (131)

Recent Advancements in the Psychology of Alzheimer's disease: -
A novel understanding of Alzheimer's disease (AD) is being advanced using neuroimaging. By detecting pathology and neurodegenerative in adults who are either cognitively impaired or not, physicians can initiate the diagnosis of the disease using imaging biomarkers.

Alterations in Epigenetics in Alzheimer's Disease: -
AD development has been linked to several epigenetic modifications, including histone posttranslational modifications, DNA methylation and hydroxy methylation, mitochondrial epigenetics (also known as Mito epigenetics), and noncoding RNA translation. [132] Numerous disorders categorized as neuropathologist, including AD, have been linked to disruption of DNAmethylation and DNA hydroxy methylation processes. [133] According to other research, the Polycomb-repressed (poised) promoter's histone signatures for H3K27me3 and H3K4me3 overlap with the distinctly methylated DNA sites in AD. [134]

DNA methylation: -
DNA methylation affects cognitive processes while maintaining basic cellular activities and synaptic flexibility in the central nervous system. The relevance of DNA methylation is further indicated by the fact that DNA hydroxy methylation is concentrated in the central nervous system and is crucial for neurodevelopment. [135] While some research revealed a general decrease in DNA methylation in AD patients, other investigations found no discernible variations in DNA methylation among AD and matched in age healthy persons. [136,137] The following genes' DNA methylation patterns associated with AD were looked into GSK3b, or glycogen kinase 3 beta, [138,139] [ANK1) ankyrin 1[140], and neurotrophic factor generated from the brain (BDNF) [141]. On the other hand, it has been observed that the prefrontal cortex and locus coeruleus have decreased in DNA methylation [142,143] and blood samples. Furthermore, research revealed that 13% of noncoding RNA CpG patterns were modified in AD patients, which significantly raised the 5mClevels in these specific genetic loci. [144]

Methylation of Mitochondrial DNA: -
Research revealed that several significant deletions in mitochondrial DNA (mtDNA) have been found and are associated with the pathophysiology of AD. [145] Low levels of mtDNA were identified in presymptomatic individuals with a PSEN1 mutation and people with AD with low Aβ and elevated tau in their cerebrospinal fluid (CSF). Low levels of mtDNA in CSF were linked to aberrant mitochondrial propagation and low mtDNA copy number, which may serve as a preclinical biomarker for AD. [146] A different study found that there was a negative association between CSF mtDNA levels and phosphorylated tau protein, but a positive link between Aβ and CSF mtDNA content. Low CSF mtDNA levels along with low Aβ and high phosphorylated tau can differentiate AD from other neurological disorders. [147] In AD blood samples, however, a notable reduction in mtDNA methylation was found. [148]

DNA hydroxy methylation: -
Studies found that elevated intragenic regions' 5hmC levels are linked to hundreds of distinct hydroxy methylated regions (DhMRs) in AD brains. The F-box and leucine rich motif protein 16 (FBXL16) gene showed elevated 5-hydroxymethylcytosine (5hmC) levels, according to genomic research. [149] A possible gene linked to AD was identified as FBXL16, which was found to have decreased encoding in mouse AD models' microglia cells. [150] An additional investigation revealed a reduction in 5hmC values in four CPG repetitions in ANK1. [149] Additional research revealed a decrease in the location of astrocytes and an increase in the deposition of tau protein [151], Although, according to one study, the AD cerebellum and entorhinal cortex do not contain 5 hmC. [152] A reduction in 5hmC deposition was

reported in the hippocampal CA1 region's AD glial cells by another investigation. [153] Subsequent research examined the role of TREM2 in AD pathogenesis and discovered a positive correlation between TREM2 expression and 5hmC repeated in exon 2, suggesting that increased gene expression could aid in tissue repair. Microglia cells include the gene TREM2, which is necessary for tissue repair, balance, and the natural immune response. [154]

Histone modification: -

Rich in arginine and lysine residues, histones (H1, H2A, H2B, H3, and H4) are highly basic proteins in biochemistry. In eukaryotic nuclei, histones act as a framework to help DNA wrap and condense, creating nucleosomes. [155,156] The homeostasis of the ageing brain, AD pathogenesis, and neuronal differentiation and growth are all impacted by histone changes. It was found that tau transgenic Drosophila, mice, and human AD all frequently lacked heterochromatin. [157] Heterochromatin relaxation and transgenic tau expression were linked to oxidative damage and DNA degradation. [158] Aberrant acetylation has been associated with aberrant signalling, apoptosis, inflammation, immunology, and neuroplasticity in histone modifications. [159]

MicroRNA: -

Several target genes for microRNAs (miRNAs) are connected to the pathophysiology of AD. Approximately 161 miRNAs may be involved in the pathogenesis of AD. Moreover, several miRNAs, such SIRT1, BACE1, and APP, were connected to the development of AD and others to the myelin sheath creation. [144] By controlling the activity of APP-degrading enzymes suchBACE1, miRNAs also have a role in the breakdown of APP and the metabolism of Aβ. [160]
Research revealed that in the early stages of AD, the encoding of miRNA-132 and miRNA212 is inhibited. [161,162] Research has indicated that there is a correlation between the overproduction of Aβ and APP and the overexpression of certain microRNAs (miRNA-155, miRNA-146, and miRNA-124). [163] Research showed that AD CNS miRNA-181 was reduced. Subsequent research revealed a correlation between increased levels of Aβ expression and the downregulation of miRNA-181. Moreover, the MAPK signalling cascade is impacted by miRNA-181 downregulation. [164] Additional studies revealed that AD CSF and blood have elevated levels of miRNA-206.

Biomarkers of Alzheimer disease: -

For an accurate diagnosis of many disorders, including AD, biomarkers are crucial tools. It is still difficult to distinguish Alzheimer's dementia from other types of dementia, even with recent advancements in diagnostic methods. Cerebrospinal fluid (CSF) analysis of Aβ-42, total tau protein, and phosphorylated tau (p-tau) is now thought to be the most reliable biological marker for the diagnosis of AD and for distinguishing it from other forms of dementia and moderate cognitive impairment. The well-known indicators for AD are decreased Aβ levels in CSF and the development of Aβ or tau deposits in AD patients' brains. [165,166,167] Additionally, biomarkers data from PET can be used to connect the underlying AD pathology to the clinical signs of dementia or MCI with varying degrees of likelihood. [168] Most of the time, family members with cognitive disorders, the patient's clinical history, and the observation of symptom progression over time are used to diagnose AD in living patients. [169] Prior to the early 2000s, an autopsy performed after death was the only reliable method of determining whether an individual had AD or another type of dementia. There are currently 12,073 biomarkers associated with AD.

About 441 biomarkers for AD diagnosis, prognosis, staging, and disease progression tracking are either authorized or in late-stage clinical investigations. The most often utilized biomarkers for AD are tau, phospho-tau, and Aβ42, which are the main constituents of tau tangles in the brain and amyloid plaques, respectively. [170] CSF, the transparent fluid that envelops and insulates the brain and spinal cord, is used to measure these biomarkers. The Lumi pulse G beta-Amyloid Ratio (142/1-40) in vitro diagnostic test was approved by the US FDA in May 2022 for the purpose of evaluating beta-amyloid pathology in CSF samples. [171]
Every suggested or authorized AD biomarker for prediction and illness diagnosis is: -

1. Amyloid beta A4 protein
2. Apolipoprotein E
3. Beta- amyloid protein42
4. Glucose transporters and hexokinases
5. Microtubule- associated protein tau
6. Presenilin-1
7. Presenilin-2
8. Presenilin-3
9. Presenilin-4

Using Network Biology Techniques in Alzheimer's Disease Research: -

It has been proposed that network biology techniques could revolutionize the search for therapeutic targets, disease biomarkers, and efficacious medications for polygenic multifactorial conditions such as AD, diabetes, cancer, and psychological disorders. But the success of prior systems biology studies has been limited by their customary focus on a particular type of omics, and AD was no different—the findings were only partially explaining the complex disease. To generate fresh multi-system and multi-target hypotheses, future research should analyze various omics data at the same time and employ new technologies, such as machine learning (ML) and artificial intelligence (AI).

Case study: -
a. Case Study Shows Lecanemab Possibly Deadly Side Effects When Usedto Treat Alzheimer's: -

Researchers present autopsy results in a notable case study that was published in the Journal of Alzheimer's Disease. The 65-year-old woman suffering from Alzheimer's disease (AD) had three open-label infusions of Lecanemab, an experimental anti-amyloid beta (Aβ) antibody drug. In this case, the patient experienced a "subacute" reaction to Lecanemab and died after just three infusions. This discovery at this stage of the therapy plan has never been published before. A brain examination revealed that the anti-Aβ treatment resulted in an as-yet-unidentified amyloid phagocytic syndrome that spread into the cerebral cortex's many small blood vessels, causing extensive cerebral amyloid angiopathy (CAA), even though autopsy revealed no significant systemic cardiovascular comorbidities. This seems to have caused haemorrhage during the attempt at stroke intervention and brought on the onset of stroke symptoms.

In this instance, the doctor made it obvious that it is quite likely that the individual's response to the anti-Aβ treatment resulted in signs and symptoms and established the basis for treatmentinduced haemorrhage, raising the risk of a potentially fatal drug interaction.

Even though this is the first case to be described that outlines the neuropathologic results in response to Lecanemab, it is impossible to think that this is a unique incident given the pattern and distribution of pathology.

b. Evaluation of the COVID-19 lockdown's impact on the early onset of Alzheimer's disease: -

Objective: - Assessing how early AD patients' cognitive deterioration progresses is the goal of this study on the impact of COVID-19 lockdown.

Methodology: -
1. The participants were patients from the Neurology Unit who had been diagnosed with mild cognitive impairment owing to AD (MCI-AD).
2. They had two years of neuropsychological evaluations, including cognitive impairment and daily activity tests.
3. They were divided into two groups: a case group (n = 21) that underwent evaluations both before and after the lockdown, and a control group (n = 20) that underwent evaluations only prior to the lockdown.

Result: -Over the course of the 2-year evaluation, all subjects had a rise in cognitive impairment and a decline in functional ability ($p < 0.05$). In fact, the group assessed under lockdown conditions exhibited even less deterioration, according to the statistical significance found between the two study groups for activities related to daily living.

C. Report on a New Presenilin 2 Mutation and Alzheimer's Disease in a 63Year- Old Patient:

The 58-year-old patient was referred to our dedicated memory clinic. After experiencing memory loss, repetitiveness, and executive function impairment for two years. An MRI examination at the age of 58 revealed mild frequent cortical atrophy. She is Caucasian and has finished two years of university study. She spoke clearly and without any semantic difficulties. Her neurological examination revealed no evidence of cerebellar damage, normal gait, minor ideomotor apraxia while performing commands for motor activities, and normal muscle tone and power.

Based on her early age and clinical presentation without any changes in personality, language, motor function, or variations, the most likely clinical diagnosis was EOAD. It was difficult to determine if the accounts were of a genuine hallucination or a misinterpretation of the objects in view. She suffered from motor apraxia, muscle rigidity, declining verbal and perceptual abilities, and dependence on others for all daily tasks during this time. She passed away from pneumonia at age 63. Her diagnosis of AD and the cause of death were confirmed by an autopsy, which also revealed

many plaques and tangles associated with congophilic amyloid angiopathy. Furthermore, the amygdala was shown to have significant Lewy Body disease. This case highlights the range of diseases that might develop in individuals with PSEN2 mutations and highlights the subsequent periods at which PSEN2 mutations may appear in patients. [172]

Future prospectus for Alzheimer disease: -

Because Alzheimer's starts 20 years or more before symptoms appear, a significant window of opportunity exists for us to potentially slow the disease's course. This finding is quite recent. Even in these presymptomatic years, scientific advancements are assisting the industry in progressing. Research on biomarkers for Alzheimer's disease, for instance, has made it feasible to identify people with brain beta-amyloid accumulation who may be eligible for clinical trials of experimental treatments intended to lower the accumulated beta-amyloid and thereby prevent or delay the onset of symptoms.

Additionally, biomarkers allow for early Alzheimer's diagnosis, allowing affected individuals to address modifiable risk factors that could impede or postpone cognitive deterioration. Because biomarkers enable clinical trials to selectively enrol participants with the brain abnormalities that experimental therapies target, they are already speeding up the discovery of new treatments.

However, a deeper understanding of Alzheimer's disease, including its causes and methods for managing, treating, and preventing it, is contingent upon additional important variables. One of these is having people in all areas of Alzheimer's research who come from different racial and cultural backgrounds. The absence of inclusivity has several repercussions.

First, sufficient data from Asian, Black, Hispanic, Native American, Alaska Native, Native Hawaiian, and other Pacific Islander populations are needed to accurately measure the impact of Alzheimer's disease today and in future in the United States. [173] Second, recent data show that older Black and Hispanic persons have a higher risk of Alzheimer's disease than older non-Hispanic White adults.

It takes more than just increasing the number of participants from underrepresented groups to achieve inclusion. It's also critical to diversify the research community and interact with underrepresented groups to get their opinions.

Enhancing inclusion in all these aspects increases the variety of life experiences that participants have and the degree to which those experiences are recognised and investigated. [174] The only way that everyone can gain from advancements in Alzheimer's science is if more people are represented in clinical trials, observational studies, and other types of research, both as participants and leaders.

III. CONCLUSION: -

In conclusion, individuals with Alzheimer's disease exhibit complex and diverse behavioural patterns.

To give the best care and support possible, family members, carers, and medicalprofessionals must work to better understand these patterns. To improve quality of life for patients and their carers, a comprehensive approach that considers individual requirements, underlying triggers, and the progressive nature of the condition is essential. In addition, greater study and cooperation within the medical field are needed to provide interventions and treatments that are more successful in controlling the behaviour patterns of individuals with Alzheimer's disease. The way Alzheimer's disease is diagnosed outside of and prior to clinical settings has completely changed because of advancements in biomarker diagnosis, symptomatology, facilitating patient enrolment in studies conducted during a far earlier stage of the illness, especially now that blood biomarkers appear to be accessible.

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