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Novel Pharmacological Approach to the Treatment of Alzheimer's Disease

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Abstract:

Alzheimer's disorder is one of the maximum devastating mind problems of aged humans It is an undertreated and under-identified disorder this is turning into a chief public health problem. The remaining decade has witnessed a progressively growing attempt directed at discovering the etiology of the disease and developing pharmacological treatmentAn overview of Alzheimer's as a disease state and its pharmacological and non-pharmacological management is provided in the paper. Caring for the person diagnosed with Alzheimer's may be taxing and thus caring for the carer is also described.Currently to be had remedies i.e. Acetylcholinesterase inhibitors (rivastigmine, galantamine, donepezil) and N-methyl d-aspartate receptor antagonist (memantine) contribute minimal impact on the disease and target late aspects of the disease. These tablets slow down the development of the disease, offer symptomatic relief but fail to achieve a definite cure.

Keywords: Diagnosis, Alzheimer's dementia, Memory loss,Neurodegenerative, Family history

Introduction:

Alzheimer's disease (AD) is the most prevalent chronic neurodegenerative disease with 5.7 million people living with the disease in the USA alone and this is projected to increase to 13.8 million people by 2050.Globally, the number of people currently suffering with dementia is estimated to be 50 million of which 30-35 million have AD.2 The risk of developing the disease is influenced by both genetic and environmental factors, however the biggest risk factor by far is age; the older you are the more likely you are to develop the disease but it is not an inevitable part of ageing. For instance, about one in 50 people aged between 65 to 69 have dementia, and this figure rises to one in five for those aged between 85 to 89. Given the global increase in life expectancy, this represents a huge societal and economic challenge with the impact extending to those living with AD, along with their caregivers and family. The disease often manifests itself initially as short-term memory loss and as the disease progresses symptoms include language problems, disorientation, mood swings and behavioral issues (agitation, sleep changes, psychosis). Eventually the disease progresses to loss of bodily function and ultimately to death.[1]

Oligomer species of aggregated Ab exert toxic effects on synaptic and cellular functions, finally leading to neurodegeneration and cognitive, as well as neuropsychiatric, symptoms. Current treatment of AD

includes cholinesterase inhibitors (donepezil, rivastigmine, galantamine), used for mild to moderate AD, and theNMDA receptor antagonist, memantine, approved for the treatment of moderate to severe ADDeveloping disease modifying drugs, able to counteract the progression of AD, is one of the biggest challenges of modern pharmacology. The new criteria incorporate biomarkers identify early stages of AD, susceptible to being treated with disease modifying drugs .[2] Neurodegenerative diseases are incurable and debilitating conditions that result in progressive degeneration and/or death of nerve cells. The massive sort of neurodegenerative diseases, in phrases of pathological character symptoms, and treatments, makes it very difficult to classify them in general terms. Alzheimer's disease (AD) and Parkinson's disease (PD) This confirmation is substantiated with inside the literature. In 2015, there have been 8 million AD sufferers global with direct and oblique charges to society of 81,800million USD , and in 2016 there were 6.1 million people with Parkinson's disease worldwide.Dementia is a main symptom of AD, along with reminiscence impairment followed bydysfunction, which is responsible for the inability to develop daily life activities Vasculardementia is pretty vital when you consider that it's far taken into consideration the second one maximum common cause of dementia in the aging population and also is thought to underlie AD.includes a decline in cognitive competencies as a result of blocking off or reduction of blood flow to the brain the alternative hand, PD with the aid of using motor is characterized signs and symptoms inclusive of bradykinesia resting tremor rigidity, and postural abnormalities, and non-motor signs and symptoms which include dementia, hyposmia, depression, and emotional changes [3].

Antidepressants, antipsychotics, mood stabilizers, anxiolytics, and hypnotics are used for the treatment of behavioral disturbance. Future directions in the research and treatment of patients with Alzheimer's disease include: applying functional brain imaging techniques in early diagnosis and evaluation of treatment efficacy; development of new classes of medications working on different neuro-transmitter systems (cholinergic Glutamatergic, etc. Each for the remedy of the cognitive defecated the remedy of the behavioral disturbances; and growing preventive methods (amyloid-peptide immunizations andinhibitors of ß-secretaseand secretase).[4]A variety of syndromes bring about the destruction and lack of cells of the worried system Giving upward push to numerous insidious however deadly neuropathies likeParkinsonism, Alzheimer's disease, Dementias, and Multiple Sclerosis. Such situations are encompassed as neurodegenerative disorders .Deeper knowledge of the induction in addition to development of neurodegenerative diseases implicated in a majority of such neuropathies.Despite numerous improvements in diagnostic strategies and the certain observe of molecules and subcellular technique underlying such conditions, the neurological issues are not well understood.[5]AD usually manifests via a revolutionary lack of episodic reminiscence and cognitive with subsequent decline in linguistic and visual-spatial abilities. Such changes are often accompanied by behavioral disorders such as apathy, aggressiveness and depression . It needs to be mentioned that there's a crucial subgroup of AD sufferers who do now no longer gift a commonly amnestic picture , manifesting non -amnestic deficits from the onset of symptoms . Structural neuroimaging, with a pat-tern of hippocampal and parietal atrophy in typical cases reinforces the diagnosis Patients who meet usual sickness characteristics, except for different instances together with vascular and fronto-temporal dementias, have a probable diagnosis of AD Definitive diagnosis of theailment is typically completed simplest via autopsy examination, whose purpose is to demonstrate histologically the neurofibrillary tangles and the senile plaques.[6] Genetic elements, inclusive of hazard elements are associated with AD. In a minority

of hereditary ailment seems so in a sample ofautosomal dominant inheritance. Chromosomes 21, 14 and 1 are related to a few familial sorts of early onset Moreover, the late onset familial forms appear to chromosomes 12 and 19 Sporadic cases, maximumcan't be defined from a genetic factor of view, despite the fact they have stated hypotheses that the actionof toxic agents or unidentified infectious affecting genetic aspects can't be defined from a genetic factor of Chromosomes 1, 14 and 21 are related to Early-onset forms These genes are related to mutations on Presenilin-1 (PS1), Presenilin-2 (PS2) and Amyloid precursor protein (APP) several research has verified that modifications in those proteins predisposes individuals to familial Alzheimer disease. Chromosomes 14 and 19 are related to late-onset forms. Chromosome 19 are connected to mutations on Apo lipoprotein E, in particular isoform 4(APOE4)Others form Of Alzheimer's dementia cannot be explained from a genetic point of view, including sporadiccases. Mutations in specific genes positioned on chromosomes 14 and 1 are chargeable for the disease Of early onset familial Alzheimer (EOAD) in a part of sufferers display penetrance (proportion of individuals that show the phenotype) about 100 % with autosomal dominant inheritance.[7]

During slight degrees of Alzheimer disease isimproved reminiscence loss impacts re-cent declarative memory more profoundly than other capacities, such as short-term, declarative and implicit memories .Recent memory continues to deteriorate in the moderate stage.

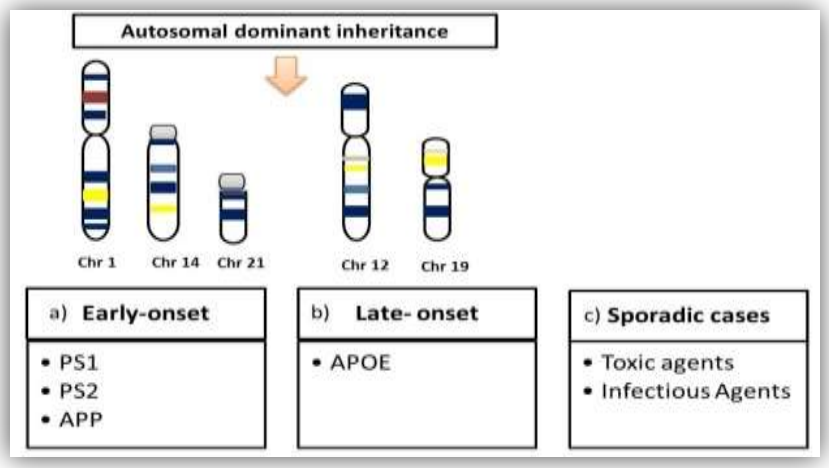

Fig :Genetic factors related to Alzheimer's dementia

Due to an inability to create new memories, Alzheimer's diseasepatients seem to live in the beyondsufferers are nonetheless capable of control primary ADLs, however assistance is required in certain beyond A longitudinal Study carried out in 1993 confirmed that it's miles at this degree that cognitive Decline , aggressive, melancholy and incontinence in sufferers grow to be predictive factors for placement in nursing homes . In the numerous stage, even early reminiscences may be lost Alzheimer's sickness is a neurodegenerative mind sickness of aged and the most commonly known cause of dementia. It is characterized by a progressive decline in based on memory, language, thinking, behavior and other cognitive skills that affect to perform daily living activities. In Alzheimer's disease, the brain cells themselves degenerate and die, causing a steady decline in mentioned cognitive,

behavioral and daily living functions. AD is devastating not only for patients, but also for the caregivers, families and community.

Definition of dementia:Dementia is a brain disorder-usually in chronic or progressive nature- in which there is disturbance of multiple higher cortical functions, including first in memory, thinking, language, visuospatial, and judgment. Cognitive impairment interferes with independence in daily living activities. Social behavioral, psychosocial impairment could proceed to dementia syndrome or could become a part of disease by course .AD is the most common type of dementia; especially for older ages more than half of the cases- and is not only a clinical phenomenon but is a definition of a distinct clinic-pathologic entity more than one century.

Preclinical, mild cognitive symptomatology and AD dementia phases the term of AD refers to a distinct ongoing pathologic process including preclinical, mild cognitive symptomatology and AD dementia phases. In spite of well-defined unique pathological hallmarks of AD- beta amyloid plaques and neurofibrillary tangles at specific localizations with progressive nature- Phenotypic presentation of sickness should various individually. The prognosis of dementia is more often than not primarily based totally on particular records of sufferers and associates. Clinical examination, laboratory and neuro-imaging investigations are mostly suitable to rule out secondary causes.[9]

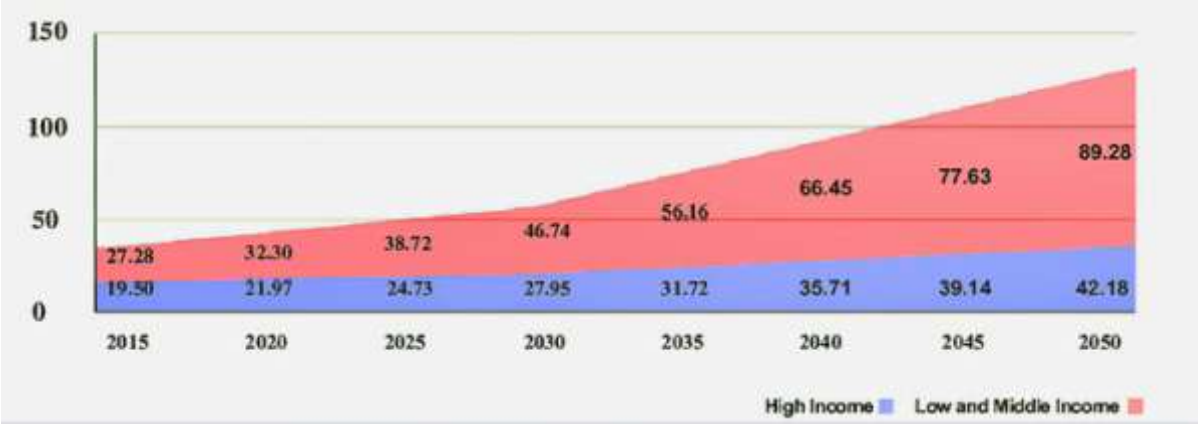

Fig 1: The boom in numbers of human beings with dementia in countries (Reprinted fromWorldAlzheimer Report 2015).[9]

Causes of Dementia:

Dementia is the loss of cognitive functioning , thinking,remembering, and . Reasoning to such a volume that it interferes with a person's day by day lifestyles and activities. It is not a disease itself, but a group of symptoms that often accompanies a disease or condition. Some dementias are treatable or curable; others are less responsive to treatment. Causes of Dementia are divided into two groups as follows:

Treatable Causes of Dementia	Other Causes of Dementia
● medication side effects ● depression ● vitamin B12 deficiency ● certain tumours or infections of the brain ● blood clotspressing on the brain ● metabolic imbalances, including thyroid, kidney, or liver disorders ● chronic alcoholism	● Alzheimer's disease ● vascular dementia ● frontotemporaldementia, including: ● ● frontotemporal dementia with parkinsonism linked to chromosome ● 17 (FTDP-17) ● ● Pick's disease ● supranuclear palsy ● corticobasal degeneration

Causes of Alzheimer's disease: The causes of Alzheimer's disease can be explained with the help of three hypotheses.

(A)Cholinergic hypothesis:

The cholinergic hypothesis of Alzheimer's disease came about due to the combined observations of deficits in choline acetyltransferase and acetylcholine (ACh) and the fact that ACh is important in memory and learning. It was thought that reduction in cholinergic neurons as well as cholinergic neurotransmission led to the decline in cognitive and non-cognitive functions.

(B)Amyloid hypothesis:

According to the amyloid hypothesis, the basis of Alzheimer's disease is the presence of Aß production in the brain The membrane protein amyloid-ß precursor protein (APP) is proteolyzed to form Aß, and it is the amyloid form of A that makes up the amyloid plaques (neurotic plaques) found in the brains of Alzheimer's disease sufferers[11] . The amyloid-cascade hypothesis was first described in 1992 by Hardy and Higgins .According to this hypothesis, Aβ and its aggregates trigger a cascade harming synapses and neurons which are responsible for the formation of pathological Aβ plaques, neurofibrillary, tangles, synaptic loss, neurodegeneration and ultimately dementia in AD. Aβ is generated by proteolytic cleavage of Amyloid Precursor Protein (APP) which is synthesized in ribosomes on endoplasmic reticulum and then transported to the Golgi apparatus. APP is a transmembrane protein. It contains an Aβ-encoding region which is cleaved by a series of secretases: α then γ, or β then γ Proteolytic processing of APP occurs by one of two pathways, the non-amyloidogenic or the amyloidogenic.[12]

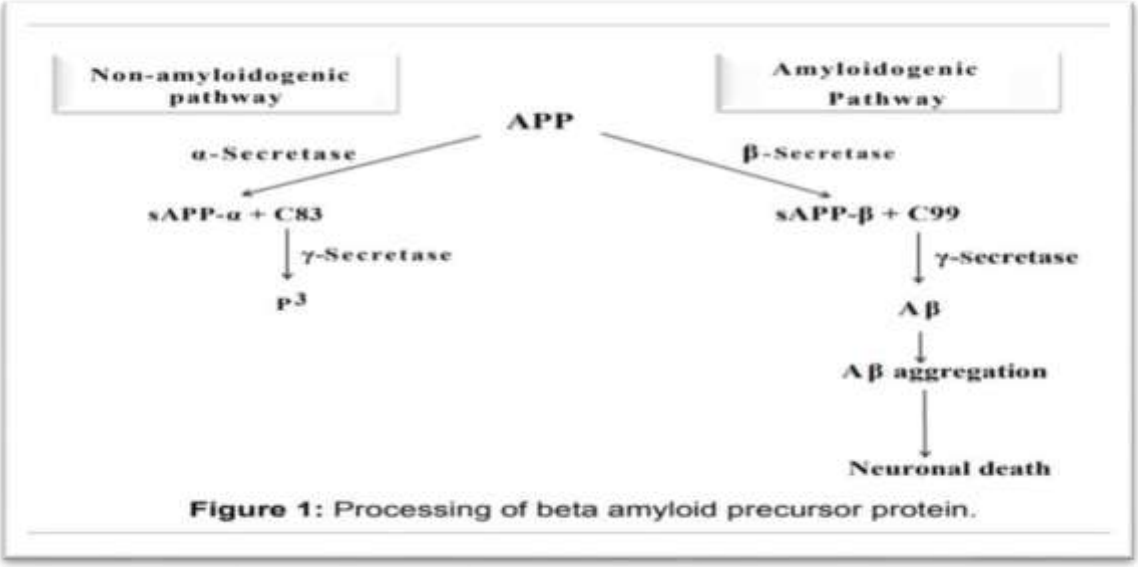

Figure 1: Processing of beta amyloid precursor protein.

Fig: Processingof beta amyloid precursor protein.

APP intracellular domain (AICD). AICD and p3 (3kDa) peptide are released into the cytosol and extracellular space, respectively. AICD can potentially translocate to the nucleus and function as aa transcription factor [13].Aβ species are formed by cleavage with β- and then γ-secretases of APP in the amyloidogenic pathway. βsecretases include β-site APP-cleaving enzyme 1 (BACE1) and 2 (BACE2). Cleavage by βsecretases releases a soluble N-terminus fragment, APPβ (sAPPβ), into the extracellular space and the remaining C-terminal fragment of 99 amino acid residues (C99) is still membrane bound. C99 is further processed by γ- secretase at the C-terminal region of the Aβ sequence, generatingAICD and an insoluble fragment, Aβ, which contains 38–43 amino acid residues. Aβ is released into theextracellular space where it accumulates and contributes to amyloid plaque formation [14].

Proteolytic degradation by the proteases, neurolysin and Insulin Degrading Enzyme (IDE), uptake by astrocytes and microglia and passive flow into the cerebrospinal fluid and sequestration into the vascular compartment by soluble form of the low-density Lipoprotein Receptor Related Protein 1 (LRP1) are the major pathways to remove Aβ peptides from the brain [15]. The degradation and clearance of Aβ from the brain have been suggested to be impaired in patients with AD [16,17]. Aβ aggregates may lead to a cascade of pathological events ranging from excitotoxicity, endoplasmic reticulum stress, oxidative stress, synaptic dysfunction, mitochondrial dysfunction, loss of calcium homeostasis and inflammation. However, amyloid-cascade hypothesis alone is not sufficient to explain AD pathogenesis as removal of Aβ did not halt AD pathology [18].

(C)Tau hypothesis:

The Tau hypothesis revolves around the presence of neurofibrillary tangles (NFTs) in Alzheimer's disease. As a result of increased phosphorylation of Tau (originally bound to microtubules), there is an increase in free tau accompanied by loss of functioning microtubules[11]. While scientists recognize that Alzheimer's sickness entails the failure of nerve cells. It's still unknown why this happens. However,

they have identified certain risk factors that increase the likelihood of developing Alzheimer's. Age: The greatest known risk factor for Alzheimer's is increasing age. Most individuals with the disease are 65 and older. One in nine people in this age group and nearly one-third of people age 85 and older have Alzheimer's. Family history Another risk factor is family history. Research has shown that those who have a parent, brother or sister with Alzheimer's are more likely to develop the disease[19]

Symptoms of Alzheimer's disease:

Alzheimer's disease is a progressive condition, meaning that the symptoms get worse over time. Memory loss is a key feature, and this has a tendency to be one of the first signs and symptoms to develop. The signs and symptoms seem gradually, over month or years. If they develop over hours or days, someone might also additionally require scientific attention, as this could indicate a stroke Symptoms of Alzheimer's disorder include:

1. **Memory loss:**

A per person may experience difficulty with reasoning son may have difficulty taking in new information and remembering information. This can lead to:

- repeating questions or conversations objects
- forgetting about events or appointments
- wandering or getting lost

2. **Problems with recognition**:

A individual can also additionally come to be much less capable of apprehend faces or objects or less able to use basic tools. These problems aren't because of issues with eyesight.

3. Problems with spatial awareness: A character may also have trouble with their balance, Trip over, or spill things more often, or they may have difficulty orienting clothing to their body when getting dressed.

4. Problems with speaking, reading, or writing: A character may also broaden problems withthinking of common words, or they may make more speech, spelling, or writing errors

Stages of Alzheimer's disease:

Alzheimer's disease can range from mild to severe The scale ranges from a state of mild impairment, through to moderate impairment, before eventually reaching severe cognitive decline.

(1)Mild Alzheimer's disease:

People with mild Alzheimer's disease develop memory problems and cognitive difficulties that may include the following:

- taking longer than usual to perform daily tasks
- difficulty handling money or paying the bills
- wandering and getting lost [21].

The growing number of plaques and tangles first damage areas of brain that control memory, language, and reasoning. It is not until later in the disease that physical abilities decline. The realization that something is wrong often comes gradually because the early signs can be confused with changes that can happen normally with aging. Accepting these signs and deciding to go for diagnostic tests can be a big hurdle for patients and families to cross[22].

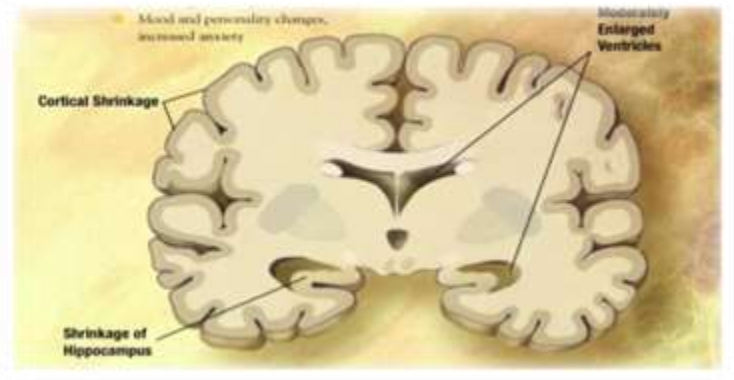

Fig: Brain condition in mildAlzheimer disease

(2)Moderate Alzheimer's disease:

Moderate Alzheimer's disease, the parts of the brain responsible for language, senses, reasoning, and consciousness are damaged. This can result in the subsequent symptoms:

•more reminiscence loss and confusion

- spotting buddies or family
- an incapacity to research new things
- problem performing

(3)Severe Alzheimer's disease:

In extreme Alzheimer's disease, plaques and tangles are present throughout the brain, causing the brain tissue to shrink

- an inability to communicate
- dependency on others for care

- being unable to leave bed all or most of the time[21].

Fig .Brain condition in severe Alzheimer's disease. [22].

Pathophysiology of Alzheimer's disease:

Pathophysiology of AD, debate goes back to the Alzheimer's time 1907 when he observed the neuropathological features of the disease i.e., amyloidal plaques and hyper phosphorylated NFTs. Several hypotheses have been put forward on the basis of the various causative factors in order to explain this multifactorial disorder[23]. Such as the cholinergic hypothesis, Ab hypothesis, tau hypothesis and inflammation hypothesis [24]. Recently it has been shown that the most commonly used Ab hypotheses, prevailing for the last two decades, does not account for the complex pathophysiology of this incapacitating disease [25].Recent studies have also highlighted the role of Ab oligomers in synaptic impairment, suggesting that these are primarily the only one among several other signals that destroy the integrity of brain functions and formations of amyloid plaques that develop in the later age appear to be rather late event According to the amyloid cascade hypothesis, the APP is normally cleaved by a-secretase and aberrantly processed by b- and g-secretases resulting in an imbalance between production and clearance of Ab peptide[26]The Aβ peptide, which has 36 to 43 amino acids, is derived From amyloid precursor protein (APP) enzymatic proteolysis, a physiologically produced protein that plays important roles in brain homeostasis[27][28].

The APPgene is placed on chromosome 21, and is the reason the better prevalence of early onset AD in individuals with 21 Trisomy (Down Syndrome) and in people withAPP gene locus duplication [a rare form of early onset of familial origin]. It is thought that overexpression of APPresults in a growth of cerebral Aβ peptide, and consequently, in its deposition [29]. Two foremost pathways for APP processing at the moment are recognized: a non-amyl[31]. The Aβ42 peptide is greater vulnerable to aggregation than Aβ40.Immunohistochemical analysesionogenic α-secretase mediated pathway and an amyloidogenic βand γ-secretase-mediated path-way. Cleavage of APP by α-secretase results in a soluble molecule, sAPPα, which probable neuroprotective function, playing important roles in the plasticity and survival of neurons and protection against excitotoxicity[30es indicate that Aβ42is initially deposited and found at higher concentrations in the amyloid plaques observed in AD patients [32]. On the

opposite the correlation among serum AÎ²42 degrees and cerebral amyloidosis is not yet demonstrated. A lower in Aβ42 tiers isdetermined in cerebrospinal fluid of AD subjects, which can be explained in part by higher deposition of β-amyloid plaques [33].

Epidemiology of Alzheimer's disease:

The incidence and prevalence of AD rise with increasing age and are higher in women in part because of their increased longevity. The incidence of AD ranges from 1% at ages 65 to 70 to approximately 4% over age 85. In the United States, the number of new cases per year is expected to triple from approximately 420,000 in 2000 to more than 1.3 million in 2050 [34]. Estimates of prevalence of AD range from the lowest figure of 3% of the population at 65 years to the highest reported estimate of 47% of people over age 85. The prevalence of AD in the United States in 2000 was estimated to be 4.5 million[35]. By 2050, this number will increase by almost threefold, to 13.2 million. In the United States, AD currently is the eighth leading cause of death, with approximately 63,000 deaths per year and a death rate of 21.8 deaths per 100,000population [36].The death rate of AD is increasing by approximately 6% per year. The median survival from initial diagnosis recently was estimated to be 4.2 years for men and 5.7 years for women [37].AD can be divided into a familial type and a sporadic type, and also into an early onset type (younger than65) and a late onset type (older than 65). The 6-month occurrence of AD withinside the popular populace seems to be 5.5% to 9%.[38].There occurrence of the disorder doubles each 10 years.AD presently afflicts almost 1/2 of the human's elderly 85 years and older. Individuals with cognitive deficit that don't meet the usually regular clinical criteria for AD, but have a substantive lower from previous tiers of cognitive overall performance with troubles in new learning, may have mild cognitive impairment. Recent research display that 40% of those people will increase AD inside three years. Early reputation of AD is essential for remedy with cholinesterase inhibitors , planning of lifestyle, and legal issues.[39].

Genetics of Alzheimer's disease:

The presence in some families of AD individuals who have an autosomal dominant inheritance pattern has allowed for the discovery of disease genes. Mutations on three genes, known as causative genes, are fully penetrant and cause aggressive forms of early-onset AD The causative genes Are the ones encoding amyloid precursor protein on chromosome 21q21(APP), presenilin 1 on chromosome 14q24 (PSEN1),and presenilin 2 on chromosome 1q42 (PSEN2).Mutations in these genes account for approximately 5% of the total number of AD cases[40]. AD can be classified by the age of onset of the first symptoms. Early onset AD affectindividuals under 65 years of age, accounting for about 4–6% of cases of AD, while the late form AD affects individuals aged 65 years or older. Besides the age of onset of symptoms, the early and late forms of AD differ in other clinical, neuropsychological, neuropathological and neuroimaging variables[41]. All those genes seem to boom the cell manufacturing of Aβ42 with the aid of using selectively increasing the cleavage of APP byβ- or-secretase.Multiple research discovered that the APOE-four allele is disproportionately represented among patients with both late-onset and early-onset AD and that the APOE-4 allele shows a dose dependent relationship with increasing risk for AD and decreasing age at onset[42]

Histone modifications in AD:

The reversible post-translational histone modifications and subsequent chromatin Remodeling play important role in regulation of memory and learning Histone proteins Undergo various posttranslational modifications including acetylation, methylation, Phosphorylation, ubiquitination, simulation and Adenosine Diphosphate (ADP)-ribosylation. Among these modifications, acetylation/deacetylation is the most extensively studied type of histone modification due to its regulating function on gene expression. Acetylation status Of histones is maintained by the opposing actions of Histone Acetyltransferases (HATs) And Histone Deacetylases (HDACs). HATs catalyze the transfer of an acetyl group from Acetyl coenzyme A to lysine residues on the N-termini of histone proteins. HDACs remove Acetyl groups from acetylated histone proteins. In general, histone acetylation is linked to chromatin decompaction and transcriptional activation. In contrast, deacetylation leads to More condensed chromatin state and transcriptional repression or silencing. HDACs are Classified into four classes as I, II, III and IV according to their sequence homology.[43] . The influence of calorie restriction on AD pathology has been examined in AD mouse models, and it has been shown that calorie restriction reduces amyloid plaques by activating SIRT1.[44]

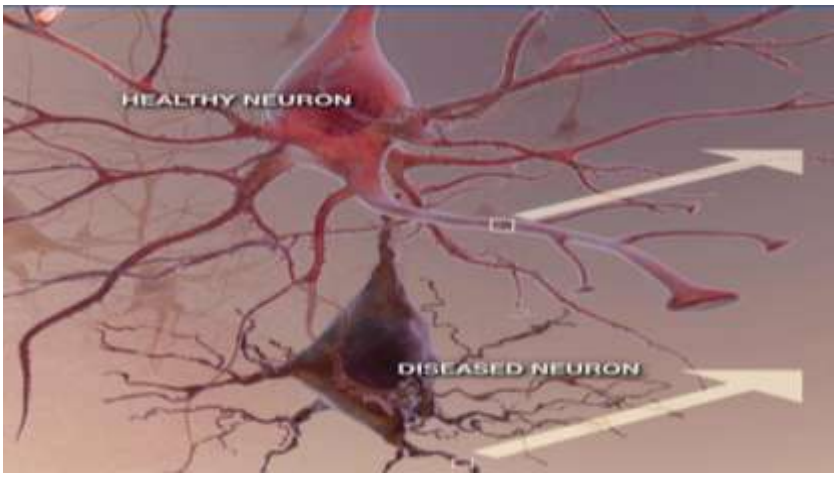

Fig : Healthy and Diseased Neuron .

Diagnosis of AD :

Doctors use numerous strategies and equipment to assist decide whether or not someone who's having memory problems has “possible Alzheimer’s dementia” (dementia may be due to another cause) or “probable Alzheimer’s dementia” (no other cause for dementia can be found). To diagnose Alzheimer’s, doctors may ask the individual and a member of the family or friend questions about overall health, past medical Problems, capacity to perform day by day activities, and adjustments in conduct and personality

- Conduct tests of memory, problem solving, attention, counting, and language o Carry out standard medical tests, such as blood and urine tests, to identify other possible causes of the problem

- Perform brain scans, such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET), to rule out other possible causes for symptoms.

These checks can be repeated to off medical doctor's records approximately how the person's memory and other cognitive functions are changing over time[45].

Steps to diagnosis of AD include:

1. Understanding the problem:

» What kind of symptoms have occurred.
» When they began.
» How often they happen.
» If they have gotten worse.

2.Reviewing medical history:

The doctor will also obtain a history of key medical conditions affecting other family members, especially whether they may have or had Alzheimer's disease or other dementias.

3. Physical exam and diagnostic tests:

A physician will:
» Evaluate diet and nutrition.
» Check blood pressure, temperature and pulse.
» Listen to the heart and lungs.
» Perform other procedures to assess overall health.
The physician will collect blood and urine samples and may order other laboratory tests. Information from these tests can help identify disorders such as anemia, infection, diabetes, kidney or liver disease, certain vitamin deficiencies, thyroid abnormalities, and problems with the heart, blood vessels or lungs.

4.Neurological exam:

A doctor will closely evaluate the patient for problems that may signal brain disorders other than Alzheimer's. The physician will also test:

- Reflexes
- Coordination
- Muscle tone and strength
- Eye movement
- Speech
- Sensation

The neurological exam may also include a brain imaging study. The most common types are magnetic resonance imaging (MRI) or computed tomography (CT). MRIs and CTs can reveal tumors, evidence of

small or large strokes, damage from severe head trauma or a buildup of fluid. Researchers are studying other imaging techniques so they can better diagnose and track the progress of Alzheimer's[46].

Diagnosis Criteria:

The clinical diagnosis of Alzheimer's disease follows a logical sequence as is observed in many diseases: the history should include information from an informantie.the person related to the patient; a mental state assessment should include a validated cognitive function test; and the physical examination should focus on vascular and neurological signs supplemented by investigations and patient history. Secondly, once dementia syndrome is recognized, the diagnosis of a subtype is important because it may determine the kind of treatment possible. syndrome does not do justice to the wide variety of symptoms and indications that make up the clinical syndrome of dementia. Activities of daily living are assessed alongside cognition, but there is less consistency in the assessment instruments used [47].

Primary Prevention of AD:

This refers to the prevention of subsequent dementia in cognitively normal subjects and is the ultimate goal for AD management. Several risk factors have been well established for AD, though some [such as age, sex and genotype] are not modifiable. Potentially modifiable risk factors which have been established through several epidemiological studies include vascular risk factors [hypertension, smoking, diabetes, atrial fibrillation and obesity] and head injury while protective factors described include use of antihypertensives, non-steroidal anti-inflammatories, statins and hormone replacement therapy[48].

Secondary Prevention of AD:

This refers to the prevention of development of AD in nondemented subjects with some evidences of cognitive impairment. The groups most often studied in this regard are those with Mild Cognitive Impairment (MCI) and several RCTs of ChEIs have been undertaken in MCI, most using conversion to dementia as the primary outcome. A meta-analysis included eight studies involving all three ChEIs, with duration of treatment ranging from 16 weeks to 3 years[49].

Treatment of Alzheimer's Disease:

Drug Therapy: There are two types of medication used to treat Alzheimer's disease: acetylcholinesterase inhibitors and N-methyl D-aspartate antagonists. The two types work in different ways [50]. Researchers hope to develop therapies targeting specific genetic, molecular, and cellular mechanisms so that the actual underlying cause of the disease can be stopped or prevented. Cognitive symptoms: Three types of drugs are currently approved by the FDA to treat cognitive symptoms of Alzheimer's disease. Three cholinesterase inhibitors are commonly prescribed:

- Donepezil (Aricept®), approved in 1996 to treat mild-to-moderate Alzheimer's and in 2006 for the severe stage.

- Rivastigmine (Exelon®), approved in 2000 for mild-to-moderate Alzheimer's.
- Galantamine (Razadyne®), approved in 2001 for mild-to-moderate stages

The second type of drug works by regulating the activity of glutamate, a different messenger chemical involved in information processing:

- Memantine (Namenda®), approved in 2003 for moderate-to-severe stages, is the only drug in this class currently available.

The third type is a combination of cholinesterase inhibitor and a glutamate regulator:

- Donepezil and memantine (Namzaric®), approved in 2014 for moderate-to-severe stages. The effectiveness of those remedies varies from individual to individual

Behavioral symptoms: Many find behavioral changes, like anxiety, agitation, aggression and sleep disturbances, to be the most challenging and distressing effect of Alzheimer's disease. possible causes of behavioral symptoms include:

- Drug side effects Side effects from prescription medications may be at work. Drug interactions may occur when taking multiple medications for several conditions.

Medical conditions Symptoms of infection or illness, which may be treatable, can affect behavior. Pneumonia or urinary tract infections can bring discomfort. Untreated ear or sinus infections can cause dizziness and pain. Environmental influences Situations affecting behavior include moving to a new private residence or residential care facility; misperceived threats; or fear and fatigue from trying to make sense of a confusing world.[51].

Future Therapeutic Approaches and Management of Ad:

Anti-amyloid agents:

The initial process of AD is not determined yet, but one of the main proposed pathophysiological processes is 'Amyloid Cascade Hypothesis'. All autosomal dominant AD genetic forms are due to mutations of amyloid metabolism encoding genes.

Although 'Amyloid Cascade Hypothesis' does not capture all aspects of disease process, there is clinical and experimental data showing toxic effects of accumulated amyloid plaques. Focused amyloid-directed therapies could be divided to three classes including secretase modulators, amyloid anti-aggregates and immunotherapies [52].

Secretase modulators:

To decrease Aβ production, research aimed to modulate enzymes that breakdown amyloid precursor protein [by stimulating α secretase or inhibiting γ and β secretase activity]. Whereas effective α secretase was infrequently identified, numerous γ and β secretase inhibitors developed. γ secretase have critical role in Aβ generation but this enzyme has multiple cleavage actions including notch receptor signaling and thought to have important side effects.

Currently developed β secretase inhibitors also failed to show disease-modifying effects but there are still ongoing researches [53]

Conclusion

Alzheimer's disease (AD) is the most prevalent chronic neurodegenerative disease with 5.7 million people living with the disease in the USA alone and this is projected to increase to 13.8 million people by 2050.Globally, the number of people currently suffering with dementia is estimated to be 50 million of which 30-35 million have AD. Current treatment of AD includes cholinesterase inhibitors (donepezil, rivastigmine, galantamine), used for mild to moderate AD, and theNMDA receptor antagonist, memantine, approved for the treatment of moderate to severe AD.

These drugs mainly provide symptomatic, short-term benefits, without affecting the underlying pathogenic mechanisms of the disease ,Ultimately, there may be a compromise because of these limitations; however, scientific understanding has given us a better picture of the course of dementia than ever before. With the advancement of technology, such as MRI and fMRI, and PET and SPET scans, used in conjunction with neuropsychological tests administered at key time points including follow-ups, the clinician is better placed to make a more reliable diagnosis and prognosis than in the past. It is hope that this will also enlighten service providers in widening access to people with learning disabilities who also have dementia.

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