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AN OVERVIEW; ON ALZHEIMER'S – DISEASE AND ITS TREATMENT

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ABSTRACT

Alzheimer's disease is most common type of dementia, it is a neurodegenerative disorder of the elderly age (above 60 age), in which decrease in memory and cognitive decline are main symptoms and other symptoms like forgetting things occasionally, decrease ability in planning, familiar task, poor judgment, depression and behavioral, psychiatric symptoms like agitation, aggressivity, delusion and hallucination. 1-4% of total population affected by AD after age of 65-70 years and 4% of total population affected by AD after age of 85 years. Actual cause of AD is not known, but it is clear that it develops because of a complex series of events that take place in the brain for long period of time. Some research shown connection between AD and head injury, genetic, environmental and life style factors. In case of AD protein beta amyloid accumulated outside neurons (called beta-amyloid plaques or neuritic plaques) and an abnormal form of the protein tau inside neurons (called tau tangles or neurofibrillary tangles) thus information transfer fails which cause impairment in memory and other symptoms. For diagnosis of AD, physical examination, patient history, modified mini-mental state examination (3MS), Cambridge mental disorder of the elderly examination (CAMDEX), blessed dementia rating scales, functional magnetic resonance imaging tests are used. USFDA approved neurotransmitter based treatments classify as cholinesterase inhibitors (ChEIs) such as tacrine, donepezil, rivastigmine and galantamine another type is N-methyl-D-aspartate in this class memantine is single drug. Other strategies are also used for treatment like anti-inflammatory agents, secretase inhibitors, insulin, etanercept, immunization, antioxidants, selegiline, hydergine, lipid lowering drugs, substances with mitochondrial impact, hormones, vitamins, minerals, nutrients and diet. Recent some alternate therapies are also used for treatment like hormone replacement therapy, stimulatory therapy, herbal therapy and herbal supplements. AD patients population increases day by day thus development of medicine is important to prevent, delay, slow or cure the disease.

KEYWORDS

Alzheimer's disease, dementia, neurodegenerative disorder and elderly age (above 60 age).

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INTRODUCTION

Nowadays our life style affect our body by rapid industrialization, changes in our life style, environmental degradation, pollution and excessive use of pesticides, herbicides and other toxic chemicals. And these chemicals / xenobiotics are toxic for our body which can cause serious life threatening hazards to our body and produces several neurodegenerative disorders, these toxins

are known as neurotoxins which affects the transmission of the chemical signals from one neuron to another and loss of neurons.

A neurodegenerative disorder of the elderly age (above 60 age) is called Alzheimer's disease (AD). AD is the most common form of dementia¹. In which decrease in memory and cognitive decline are main symptoms². In 2013 the American Psychiatric Association released the fifth edition of the DSM Diagnostic and Statistical Manual of Mental Disorder (DSM-5), which incorporates dementia into the diagnostic categories of major and mild neurocognitive disorders. To meet DSM-5 criteria there should be major neurocognitive disorder or a major cognitive decline, an individual must have evidence of cognitive decline for example, decline in memory, language or learning, and the cognitive decline must interfere with independence in daily activities of patient³.

Types of dementia

Following are the type of dementia.

Alzheimer disease- (synonym-Monogenic Alzheimer's disease)

Alzheimer disease is most common type of dementia, 60 to 80 of all cases. There are several stages of Alzheimer Disease with different symptoms in every stage. In early stage of alzheimer there are several symptoms like difficulty in remembering recent conversations, name or events and depression. In later stage impaired communication, disorientation, confusion, poor judgment, behavior changes and at last difficulty in speaking, swallowing, and walking. In 1984 Alzheimer's association and National Institute of neurological disorders and Stroke proposed guideline and diagnostic criteria for Alzheimer's which was further updated in 2011 by the National Institute on Aging (NIA) and the Alzheimer's Association. NIA and Alzheimer's Association proposed new guidelines for helping in categorizing and pathologists describe the changes in brain during the Alzheimer's disease in 2012. It is concluded that Alzheimer is a brain disease which develops slowly. It is reported that Alzheimer's disease caused by accumulation of the protein fragment beta-amyloid (plaques) outside the

neurons and twisted strands of the protein tau (tangles) inside neurons which cause damage and death of neurons⁴⁻⁹.

Vascular dementia-

Vascular dementia is less common than Alzheimer, only about 10% cases. It is considered as second most common cause of dementia after Alzheimer's disease. Vascular dementia is a fall in thinking skills and less supply of oxygen and other nutrients due to decreased blood flow to brain, blockage or damage of blood vessels or bleeding in brain. It is commonly seen in older individual. Most of cases it coexist with AD, when two or more type of dementia present at same time it is called as mixed dementia. symptoms of vascular dementia are poor ability to judge, make decision, plan, organize and change in thinking skills, these symptoms sometimes occur suddenly when major blood vessels block⁴⁻¹².

Mixed dementia

In which more than one type of dementia occurs simultaneously. In mixed dementia symptoms depends on the brain changes occurs and brain regions affected. Most common example of mixed dementia is Alzheimer with vascular dementia and other are Alzheimer's with DLB, vascular dementia with DLB (less common) and Alzheimer's with vascular dementia and DLB.

Dementia with Lewy bodies

It caused by abnormal microscopic deposits (protein alpha- synuclein) in the brain cell that damage brain cells, when they developed in cortex part of brain it produce DLB which affects decline in thinking, reasoning, and other independent functions. In case of Parkinson's disease protein alpha synuclein deposited but location in brain is substantianigra which cause neuronal loss same as DLB. Some symptoms in DLB patients seen as AD and some other are sleep disturbance, visual hallucination and slowness. But many time AD occur with DLB, and there symptoms emerge and cause misdiagnosis, it also coexist with vascular dementia.

Frontotemporal lobar degeneration (FTLD)

FTLD is a group of disorder such as primary progressive aphasia, Pick's disease, corticobasal degeneration and progressive supranuclear palsy.

Degeneration in brain's frontal lobes (the areas behind the forehead) or temporal lobe (the regions behind the ears) is affected in FTLN, the nerve cells of these regions are shrunken (atrophied) in case of FTLN and upper layer of cortex part of brain developed soft and spongy. Changes in personality and behavior and difficulty with producing or comprehending language are early symptoms¹⁰⁻¹².

Normal pressure hydrocephalus

It is brain disorder in which excess cerebrospinal fluid accumulates in the brain's ventricles, due to impaired reabsorption of cerebrospinal fluid, which increase pressure in brain. Sometimes it treated by drain of excess fluid using surgical installation of shunt.

Symptoms of normal pressure hydrocephalus include thinking and reasoning problems, difficulty walking and unable to control urination.

Creutzfeldt-Jakob disease

It is very rare disease. Disease caused by formation of misfolded protein (prion) or be hereditary by which it destroy brain cells, other protein throughout the brain and malfunction, it is also known as prion disease. It is fatal brain disorder which impairs memory, behavior changes, decrease in thinking and reasoning, uncontrolled muscle movement, confusion, difficulty in walking and mood swing.

Parkinson's disease (PD)

In PD, in substantianigra part of brain, alpha synuclein aggregates appear in deep which cause degeneration of nerve cell the produces dopamine, and brain change spread, mental function affects, including memory, ability to pay attention, judgment, plans, problem with body movements (slowness, rigidity, tremor and change in gait) are common symptoms. PD is about one 10th of AD¹⁰⁻¹⁵.

Huntington's disease dementia

It is rare type of dementia and progressive brain disorder which is caused by a defective gene. It affects movement, mood and thinking skills due to changes in the central area of the brain.

Down syndrome dementia

Down syndrome seen in those people born with extra genetic material from chromosome 21, one of

the 23 human chromosomes. With the aging process, the patients with Down syndrome are at a higher risk to develop dementia type which is extremely similar with AD or is the same.

Korsakoff syndrome

It is occurs due to severe deficiency of thiamine (vitamin B-1) and cause chronic memory disorder. Common cause of korsakoff syndrome is alcohol misuse, but certain other conditions can also cause this type of dementia.

Posterior cortical atrophy (PCA)

PCA cause progressive degeneration of the cortex (outer layer of brain) located in the back of the head (posterior). It is not distinguish PCA a possible variant from AD or a unique disease¹¹.

Many diseases are known to cause dementia and the term dementia does not imply a prognosis. Types of dementia, some dementias are fully treatable, some are partially treatable, and others do not have effective treatment at the present time. Therefore, dementia is important to accurately diagnose. Alzheimer's disease is the most common type of dementia, which was first recognized by Alois Alzhiemer in 1906¹.

AD is a brain disease which is irreversible and progressive that slowly destroys memory, thinking skills (unability to think) and drastically affects the social and behavioral skills, even the patient not capable to carry out simplest tasks, it imparts great financial burdens on patient, families, and community.

AD was once considered as a rare disease but our recent life style increase the chances of AD and seen as a major public health problem, which affects millions of older peoples¹⁶.

Symptoms of Alzeimer's disease

Alzheimer's disease affects people in different ways. Decrease ability to remember new information is a common symptom of AD. Because Following are common symptoms of AD
Memory loss that disrupts daily life. Forgetting things occasionally.

Decrease ability in planning or solving problems.

Difficulty completing familiar tasks at home, atwork or at leisure.

Confusion with time, place, name.

Trouble understanding visual images and spatial relationships.

New problems with words language or writing.

Misplacing items and losing the ability to retrace steps.

Decreased or poor judgment.

Withdrawal from work or social activities and loss of motivation.

Changes in mood and personality, including apathy and depression.

Not managing self care¹⁷⁻¹⁹.

Patients may exhibit symptoms of depression in the early stages.

Behavioral and psychiatric symptoms like agitation, aggressivity, delusions, and hallucinations may develop, in later stage²⁰.

Epidemiology

At the time when disease discovered by first Alois Alzheimer, it was considered rare and attracted little scientific interest because few people reached to greater risk²¹. It is mostly seen and common form of dementia, 1% to 4% of total population affected by AD after age of 65-70 years and 4% of total population affected by AD after age of 85 years (DeKosky, 2001). The pathology was thought to be arteriosclerotic of AD. But Corsellis and Evans (1965) and Tomlinson, Blessed and Roth (1970) found that there were no arteriosclerosis in patients suffering with a late onset Alzheimer's disease²². Several organizations give AD epidemiology data after a time interval, few data are as follows

According to the National Institutes of Health (NIH) estimates that 4.5 million Americans are affected by AD, at an annual cost of \$100 billion per year. More research estimates that in the year 2050, 13.2 million older Americans are expected to have AD no preventive treatment becomes available¹.

Research by World Health Organization, above age of 60 years 5% of men and 6% of women affected with Alzheimer's type of dementia worldwide.

Alzheimer's disease International reported that 35.6 million people living with dementia worldwide in 2010, and this increase to 65.7 million by 2030 and 115.4 million by 2050²³.

Stages of AD

AD become worse with time, experts describe several stages for AD, it describes some common patterns of disease which are as follows.

Stage 1:

No impairment (Normal behavior)

Patient and medical professional did not show any symptoms of memory loss.

Stage 2:

Very mild decline (minor memory lapse)

At this stage patients experienced memory loss with his or her familiar things like words location. But no symptoms experienced by medical exam, family and friends. These symptoms may be normal change due to age or it may be signs of Alzheimer's disease.

Stage 3:

Mild cognitive decline

At this stage AD may be diagnosed in some patients during medical interview but it is difficult to notice by friends, family at this stage. There is confusion in familiar things and loss of names.

Symptoms at this stage may:

Valuable object may be misplaced or lost by them

Trouble with planning or organizing things and remembering names when meet with new people.

Serious problem seen with right word or name and performing tasks.

Forgetting once they read

Stage 4:

Moderate cognitive decline

At this stage an interview with medical professional shows difficulty in many things which are as follows.

Forgetfulness of recent events

Unable to recall about one's own personal history

Paying bills or management of home finances, more difficulty with these type of complex tasks.

Difficulty with normal counting or arithmetic.

Behavioral changes like mood swing.

Ability to perform challenging mental arithmetic is impaired such as backward counting from 100 by 7s

Stage 5:

Moderately severe cognitive decline

At this stage patient need help in daily routine day by day. Thinking and gaps in memory is noticeable.

Symptoms at this stage may:

Confused over where they are and what day it is?

Having problems in solving less challenging mental arithmetic for example backward counting from 40 by subtracting fours / from 20 by subtracting twos.

Forgetting their common things like own address, phone number or where they completed their education.

At this stage patient able to remember significant details about themselves and family, and not for eating and using toilet patient not require assistance.

They need help for proper clothing according to occasion and season.

Stage 6:

Severe cognitive decline (Moderately severe / mid-stage)

At this stage several changes take place related to personality, sleep patterns (sleeping during day and restless at night). Patients memory continues to worsen day to day. Difficulties with stage 6.

Able to remember their own name but difficult to remember their own history. They can't even remember the name of their caregiver and can't distinguish familiar and unfamiliar faces.

Become lost and lack of awareness of surrounding and recent experiences.

Trouble with controlling their bladder or bowel, they need help because they make mistakes without supervision in small issues such as footwear on wrong feet, putting pajamas, and for toilet (flushing the toilet, wiping or disposing of tissue properly).

Changes in behaviors which includes delusion and suspiciousness (such as believing the caregiver is fake) / feeling compelled, persistent behavior such as hand-wringing or tissue shredding.

Stage 7 - Very severe cognitive decline (Severe or late-stage Alzheimer's)

In this stage of AD patients need daily personal care such as eating or using toilet. They are unable to sit without support. Reflexes don't work properly. They lose the ability to smile, respond to the environment, swallowing, conversation with people, difficult to control the body movement and muscles become rigid^{1,25}.

Cause of Alzheimer

In the 1960s and 1970s, researchers observed that patients with psychiatric disorders affected by herpes simplex virus type 1 (HSV-1). Later by using these results, Sequiera *et al* studied that HSV-1 nucleic-acid sequences in the brain of dementia and psychiatric patients, and they observed that the HSV-1 genome was present in brain samples of elderly patients with dementia. Some other groups also searched for a causal relationship between late onset sporadic AD and viral infection, but many of them failed to show any connection. They investigated various kinds of viruses, including HSV-1 and HSV-2, measles virus, adenoviruses, cytomegalovirus (CMV), poliovirus, hepatitis B virus, and influenza virus A and B. Renvoize *et al* and Renvoize and Hambling measured serum antibody titers to CMV, adenovirus, chlamydia group B, *Coxiella burnetii*, HSV, influenza A and B, measles virus, and *Mycoplasma pneumoniae* in AD patients, and no association seen, these negative results may be attributable to the recent methodologies used. Other researchers provided evidence for the presence of HSV genomes, using the polymerase chain reaction (PCR) in AD patients. Previously, spirochetes were also investigated as a potential risk factor of AD. Two other bacteria, *Chlamydia pneumoniae* (*C. pneumoniae*) and *Helicobacter pylori* (*H. pylori*), recently reported for AD.

Reports show that few types of infectious agents like *C. pneumoniae* and spirochetes, can be detected in the brains of AD patients, near senile plaques or neurofibrillary tangles (NFTs). Senile plaques and tangles are not only characterized in the brain, but also by inflammatory responses and oxidative reactions reported in AD patients' brain. There is evidence that aging factor that contributes to inflammation in the brain as a causative agent of AD, and it may be reasonable to hypothesize that infection with pathogens may cause an inflammatory response and increased oxidation²⁰.

Other studies also show that the risk factors related to AD, age is one since a great number of AD cases appear as individuals age. After 65 in the United States is approximately 6–10%. The main

risk factor is aging, with common rates doubling after every 5 years from a rate of 1–2% in the 65- to 74-year-old age group, to 25% and over in subjects 85 years and older. The age-related factors that cause Alzheimer's disease are currently not known. But it is known that after age 40, protein beta-amyloid builds up in cerebral blood vessels. In Alzheimer's disease, Beta-amyloid protein is found and it is believed to be for its pathogenesis which cause inflammation and oxidation².

Scientists don't yet fully understand what an actual cause of AD is, but it is clear that it develops because of a complex series of events that take place in the brain for long period of time. Some research has shown a connection between Alzheimer's disease and head injury. And other causes include genetic, environmental, and lifestyle factors²⁶.

A family history of Alzheimer disease (Payami et al., 1977; Katzman et al., 1989; Graves et al., 1990b; Brayne, 1991; Graves et al., 1991; van Duijn et al., 1991; van Duijn and Hofman, 1992; Fratiglioni et al., 1993; Canadian Study of Health and Aging Working Group, 1994b; Forster et al., 1995).

The presence of the apolipoprotein E gene-e4 allele (Payami et al., 1977; Brayne, 1991; Fabian et al., 1996; Kukull et al., 1996; Treves et al., 1996; Bickel et al., 1997; Evans et al., 1997)

Many diseases can cause Alzheimer such as Patient suffering from depression (Brayne, 1991; Jorm et al., 1991; Kokmen et al., 1991; van Duijn and Hofman, 1992; Speck et al., 1995), Down's Syndrome (Brayne, 1991; van Duijn et al., 1991), and race (Schoenberg et al., 1985) are all genetic factors that are likely to influence of the disease. Other controversy factor such as hypertension (Kokmen et al., 1991), low serum vitamin B12 (McCaddon and Kelly, 1994), and vascular disease (Blass, 1993).

Other suspected factors that causes AD are.

Head trauma with loss of consciousness (Chandra et al., 1989; Katzman et al., 1989; Graves et al., 1990c; Brayne, 1991; Mortimer et al., 1991; van Duijn et al., 1992; Mayeux et al., 1993; Mortimer and Graves, 1993; Canadian Study of Health and

Aging Working Group, 1994b; Rasmusson et al., 1995; Schofield et al., 1997).

Other environmental factor lower education connection with depression is a risk (Beard et al., 1992; Henderson et al., 1992; Mortimer and Graves, 1993; Canadian Study of Health and Aging Working Group, 1994b; Mortel et al., 1995; Ott et al., 1995; Yoshitake et al., 1995), smoking factor (Katzman et al., 1989; Brayne, 1991; Graves et al., 1991; van Duijn and Hofman, 1991; van Duijn et al., 1992; Brenner et al., 1993; Lee, 1994; Forster et al., 1995; Yoshitake et al., 1995; Lerner et al., 1997), aluminum absorption (Martyn et al., 1989; Graves et al., 1990a; Forbes et al., 1991; Forster et al., 1995; McLachlan et al. 1996; Gun et al., 1997), electromagnetic fields (Sobel et al., 1995, 1996; Sobel and Davanipour, 1996)², zinc²⁶, some factor provoke controversy include maternal age at birth (Katzman et al., 1989; Graves et al., 1990b; Hofman et al., 1990; Brayne, 1991; Rocca et al., 1991b; van Duijn and Hofman, 1992; Fratiglioni, 1993; Fratiglioni et al., 1993), occupational exposure to solvents and glues (Shalat et al., 1988; Brayne, 1991; Canadian Study of Health and Aging Working Group, 1994b; Kukull et al. 1995; Gun et al., 1997), gender (Schoenberg et al., 1985; Katzman et al., 1989; Jean et al., 1996), antacid consumption (Graves et al., 1990a), alcohol consumption (Brayne, 1991; Graves et al., 1991; Fratiglioni et al., 1993; Yoshitake et al., 1995)². Alzheimer with family link, called familial AD.

It is caused by mutations in three genes

Genetic fault on chromosome 21 in a gene amyloid precursor protein (APP), this fault affects the production of amyloid. Production of this amyloid protein in the brain is a risk factor for Alzheimer disease.

Genetic fault on chromosome 14 (presenilin-1, PS1), mutation in PS1 causes familial AD.

Genetic fault in chromosome 14 (presenilin-2, PS2). These mutation results increased production of Amyloid β 42 peptide (A β 42), which is involved in pathogenesis of disease. The mutations increase production of toxic A β 42 peptide over the shorter, less toxic A β 40 peptide by shifting the cleavage site to favor the γ -secretase site²⁶⁻³⁰.

Pathophysiology

100 billion neurons, found in a healthy adult brain with long and branching extension. These extension forms connection between neurons, these connection are called synapses, information transferred from one neuron to another. Brain contains about 100 trillion synapses, It is network of information in which signals are flow, which is responsible for memories, thoughts, sensations, emotions, movements and skills. In case of AD it is reported that the protein beta-amyloid *outside* neurons (called beta-amyloid plaques or neuritic plaques) and an abnormal form of the protein tau *inside* neurons (called tau tangles or neurofibrillary tangles) accumulated. This beta-amyloid deposition affects to several factor neuron to neuron communications, neurons and synapses functioning affected, thus information transfer fails at synapses, the number of synapses decrease, and neurons/cell death occur which cause impairment in memory and other activities and it also cause inflammation and oxidative stress. Supply of nutrients and other essential molecules in the neuron blocked by Tau tangleskwonw as microtubular dysfunction which cause cell death. AD patient's brain shows neuron death and shrinkage of cell. Astrocytes, microglia, and other inflammatory components activated by amyloid which cause further damage. response, leading to further damage. In cortical association areas and medial temporal lobe, the pathologic changes on plaques and tangles often start that are projected back to the nucleus basalis in which the maximum cholinergic neurons are situated. Subsequent due to decrease number of cholinergic neuron neurotransmitter acetylcholine is decreased which is responsible for memory, which cause neurotransmitter abnormality in this disorder. In other hand, loss of serotonergic and adrenergic neurons occur which cause psychiatric and changes in personality, loss of somatostatin also reported but the significance is unknown at this time^{2,19}.

There is proved risk Genetic Mutations for Alzheimer's disease. An abnormal change in the sequence of chemical pairs which is responsible for make up of genes known as genetic mutaion. These mutations involve the gene for the amyloid

precursor protein and the genes for the presenilin 1 and presenilin 2 proteins. It is observed that some families inheritance of Alzheimer's disease with mutation of chromosome 21, that encodes the amyloid precursor protein and Other mutations of chromosomes 1 and 14, encoding for presenilin proteins. 1 percent or less cases of AD estimated which caused by mutations in any three genes. An individual will develop Alzheimer's disease is further guarantees if any of these genetic mutation are inherited. In such individuals, disease symptoms develop very early before age 65, sometimes as early as age 30, late-onset disease, occurring at age 65 or later^{2,31}.

Diagnosis

AD diagnosis is tough task because there is no specific biological marker for the disease. Single way to diagnose AD is by histological examination of the brain tissue, which can only possible after death. Nowadays early diagnosis of dementia is increased because treatments are now available which delay onset and slow progress of disease so early method of detection is important. The "probable" diagnosis are done with the help of clinical criteria which is the definitive diagnoses are only made by autopsy. In clinical criteria, clinical feature of disease diagnosed like loss in memory and other cognitive functions like language difficulties (aphasia, anomia), problem in visualspatial skills (agnosia) and motor spatial skills (apraxia). First symptom of AD is short-term memory, patients forgetting what happened yesterday or even before few hours, other symptoms like repeats stories, misses appointments, and loses objects. Than Long-term memories decline reported. At the end stage the patient may be totally mute and even can't spoken language.

A recent research by Bookheimer *et al* for AD occur by genetic mutation shows that combining genetic and neuroimaging may prove important for diagnosis in the coming years. Neuronal changes and pathology occur in Alzheimer's disease years before clinical symptoms present elevated by this research. This study done in two groups of human model, one group of persons with high risk for AD based on genetic data and other group of persons

with no genetically risk. Both group performed memory tasks during which brain activities are measured by functional magnetic resonance imaging (fMRI). Both groups were scores on memory testing and normal on neurologic examination but activation increased with genetic risk of AD persons. It is reported that person with genetic risk needs more efforts for same task or same level of performance.

AD patients diagnosed by physical exam, patient history, cognitive and psychological tests. Screening test are used for overall mental examination mini-mental state examination (MMSE) (Folstein *et al.*, 1975), or the modified mini-mental state examination (3MS) (Teng and Chui, 1987; McDowell *et al.*, 1997) and some other instrument are mostly Cambridge mental disorders of the elderly examination (CAMDEX) (Roth *et al.*, 1986), Blessed dementia rating Scales (Blessed *et al.*, 1968).

For differentiate between vascular dementia, mixed dementia and ADHachinski ischemia scale (Hachinski *et al.*, 1975) is used. It is difficult to diagnose between AD and VaD in both spectrum of heterogeneity is seen by which difficult in clinician to exclude the vascular contributions to AD. Due to lack of sensitivity of instrument some AD cases are remain undiagnosed, for diagnosis of disease progress instrument such as global deterioration scale (GDS), the clinical dementia rating scale (CDR) and MMSE are used, these instrument very helpful to classify disease stages^{2,20}.

Treatment

AD is known as brain amyloidosis. The main target of the treatment in AD patients is prevention of deposition of amyloid beta protein. Several neurotransmitters like cholinergic, noradrenergic, dopaminergic, and GABAergic decreased in AD. The United States Food and Drug Administration (USFDA) has approved neurotransmitter-based treatments to improve the symptoms by increasing the level of neurotransmitters which classify as cholinesterase inhibitors (ChEIs) such as tacrine, donepezil, rivastigmine and galantamine, these drug show their action by reducing the degradation of acetylcholine in the synaptic cleft which maintain

the synaptic transmission. Another type is N-methyl-D-aspartate in this class memantine is a single drug. Memantine blocks N-methyl d-aspartate (NMDA) receptor. Education about the treatment is essential for patient compliance for an effective treatment. Effectiveness of these drugs varies from patient to patient. Proper management for the effective treatment is necessary; Active management includes

Coordination with physicians, other health care professionals and other caregivers, proper use of available treatment options,

Coexisting conditions should managed,

Taking part in supportive groups and services, and participation in activities and/or adult day care programs³²⁻³⁴.

Cholinesterase inhibitors (ChEIs)

Tacrine

It is first drug approved for AD, but rarely used today because it cause hepatotoxicity. All the drug of this class having same efficacy, drug choice based on cost, preference of doctor, and patient tolerability.

Donepezil

It is a reversible and noncompetitive cholinesterase inhibitor (ChEI) prescribed commonly for the treatment of AD. It prevents by the breakdown of acetylcholine in the brain. It cause some side effects like nausea, vomiting, anorexia, muscle cramping, sleep disturbance and diarrhea. It is FDA approved drug. A general dose for donepezil is 5 mg/day for four weeks, then 10 mg/day, after three months on 10 mg, a dose of 23 mg may be prescribed, but for most patients remain on the 10 mg dose.

Rivastigmine

The rivastigmine (Exelon) was approved by USFDA in 2006 for used in the treatment of AD (capsules and liquid formulation). It is a dual inhibitor of acetylcholinesterase and butyrylcholinesterase. Doses ranging from 6 mg/day to 12 mg daily are having with greater efficacy. The starting dose of Rivastigmine is 1.5 mg twice a day with food; if it well tolerated dose should be this titrated in 3 mg/day increments every 2-4 weeks. For providing continuous drug delivery and preventing

fluctuations in drug serum concentration as seen with oral therapy, transdermal rivastigmine is also FDA approved, which also reduce side effects and increases adherence to the drug. The most common side effects of rivastigmine include nausea and vomiting, particularly during the titration phase.

Galantamine

Galantamine used for the treatment of patients with mild to moderate Alzheimer's disease and FDA approved. Galantamine shows action by inhibition of acetyl cholinesterase, and may also modulate presynaptic nicotinic receptor activation, which increasing neurotransmitter concentrations in the synaptic cleft, prevents from AD².

N-methyl-D-aspartate (NMDA)

Memantine

Overstimulation of the NMDA receptor by glutamate (principal excitatory neurotransmitter), this overstimulation cause neuronal damage and this phenomenon known as excitotoxicity. This excitotoxicity results as neuronal calcium overload. Stimulation of NMDA receptor by glutamate particularly affects memory, cause dementia and AD.

Memantine is a new drug having low to moderate affinity, noncompetitive NMDA antagonist and reduces glutamatergic excitotoxicity. It is approved by the FDA for the treatment of moderate to severe stages of Alzheimer's disease. Low to moderate affinity is very important property of Memantine, because some other NMDA receptor antagonists having high affinity like ketamine and amantadine but they show neuropsychiatric side effects. Memantine is generally well tolerated. It blocks effects of glutamate activity that cause neuronal cell death. Most common side effect is dizziness. The daily dose of memantine is 10 mg twice daily, achieved by a 3-week, three-step, and titration schedule starting with 5 mg daily. A 20 mg once daily preparation has recently been introduced^{2,35}.

Other strategies

Anti-inflammatory agents

Anti-inflammatory drugs that interfere with aspects of the microglial, astrocytic, and cytokine responses found in the brain of a patient with AD, it is another

approach that can be used to treat AD. A study shows that persons regularly taking nonsteroidal anti-inflammatory drugs for 2 years or more had a 60% less chance of getting risk of Alzheimer's disease because these drugs have the nature to reduce the cell death due to inflammation. These anti-inflammatory drugs are more recommended for prevention rather than treatment of AD. A research on an animal model shows that oxidative stress reduced by anti-inflammatory cyclooxygenase-2 (COX-2) inhibitors (rofecoxib) but non-specific COX inhibitors (flurbiprofen and ibuprofen) did not. Another research shows that naproxen, and a COX-2 (MF-tricyclic) inhibitors each restored memory, but only MF-tricyclic blocked the suppressive effect of β A on synaptic plasticity. AD is reduced by ibuprofen and lesser by indomethacin, while celecoxib and salicylates having no protective activity. A research on a human model celecoxib a COX-2 inhibitor, improved memory and cognition in individuals with mild cognitive impairment^{2,35}.

Secretase inhibitors

Secretase is an enzyme found in the cell membrane which breaks Amyloid precursor protein (APP). A research on an animal model shows that Beta-secretase inhibitors reduce β A in animal models with fewer adverse effects. Memantine is a beta-secretase inhibitor drug used in early development stage which also decreases β A and inhibits AChE production.

Insulin

Insulin has major roles in the functioning of cells and has many roles in normal. Insulin improves memory in AD subjects by nasal administration; by this route insulin reaches the brain quickly without affecting other body parts which reduces the side effects. The verbal memory was improved by the nasal administration but this is specific only for the persons with a particular type of genetic makeup. Other organs as well as the brain are affected by insulin resistance, so it becomes difficult to acquire energy for maintaining cells and synaptic connections for the brain cells, and hence the death of cells can take place. It has been found that hyperinsulinemia increases inflammation. The formation of poisonous protein fragments known as beta-amyloid derived

diffusible ligands is a possible mechanism for the insulin resistance in the CNS. This theory states that ADDLs link to the receptor sites in the synapse where they prevent insulin from working cause eventual dementia and synaptic dysfunction.

Etanercept (Enbrel[R]) (TNF- α modulator)

Recently it observed that Etanercept produce improvement in cognitive. In case of AD high level of the cytokine TNF- α found in the brain. This TNF- α regulates neural transmission. And this TNF- α level reduced by etanercept spinal injection³⁵. Weekly treatment with etanercept 25-50mg over 6 months gives improved effects in AD, etanercept is approved for immune disorder not for AD by FDA³⁶.

Immunization

It is observed that when we inject AN1792 (synthetic form of β A) it reduce Beta amyloid (β A) in AD patients. This reduce β A, how effect AD is not clear. Certain people react to immunization with the show progression of the disease that might be after 46 years even, while in other studies it has been found that a clearing beta-amyloid deposits the chain of events can not stopped which is probably started by the beta-amyloid accumulation.

Active and passive both immunization strategies are used for AD. Three basic mechanism which benefits active and passive immunization have been proposed.

Small amount of anti-Abprotein antibodies may cross the blood-brain barrier reaches to brain, and bind to Ab protein, and forms Ab protein antibody complex. This complex cleared by local microglia.

Anti-Ab protein antibodies have high concentration in the peripheral circulation may bind to Ab protein in peripheral compartment, which redistribution the Abprotein from brain parenchyma to cerebrospinal fluid to plasma.

The anti-Ab protein antibodies neutralize synaptotoxic effects by binding to soluble Abprotein oligomers in the brain (Bard *et al.*, 2000). There strategies proven in mouse model of AD but it is not clear how antibodies shows these effects.

Antioxidants

Accumulation of Ab protein in neurons prevented by various antioxidants like, calcium channel

blockers, metal chelators, or modulators of certain signal transduction pathways. In this treatment neurons response to the Ab protein it is a major problem for this treatment and its related to inflammatory process in several ways. By blocking these one or two these response pathways might not overall neuronal dysfunction and loss. A test shows that chelator of copper and zinc ions may reduce cerebral b-amyloid protein levels in AD patients (Cherny *et al.*, 2001). The risk of AD can be reduced high intake of vitamins C, E, B6, and B12, and folate unsaturated fatty acids, and fish but the results of different reports are not compatible with each other³².

Selegiline

It improves cognitive deficiency by increase levels of catecholamine and adrenergic stimulation. Selegiline is a monoamine oxidase inhibitor which is a antioxidant used for parkinson's disease, many studies shows its helpful affects in AD (Sano *et al.*, 1997), grater numer of studies shows favourable effects in memory enhancement, and other AD factors. But authors of meta-analysis of 15 clinical trials concluded that there was not enough proof to approve selegiline as a treatment for AD in 2000. Because there are some the risk factor of stupor, rigidity, hypotension, severe agitation, and elevated temperature. And this therapy also contraindicated in patients who are taking tricyclic antidepressants or meperidine cause seizures and death, and precaution taken for other opioids. Now the use of selegiline restricted for use in AD (Standridge, 2004)^{2,32}.

Hydergine

Hydergine is a drug used to treat dementia specially AD. It improves cognitive impairment. It is a mixture of methanesulfonatesalts or ergoloidmesylates which used for enhancement of memory impairments several double blind studies shows that. Currently there is some evidence against the use of hydergine in AD, by recentmetaanalysis conclude that there were no improvements in neuropsychological, behavioral and related to memory with hydergine².

Lipid-lowering drugs

The relationship between AD and cholesterol is strengthened by the discovery, that apolipoprotein E (ApoE), a gene and protein participating in the transport of cholesterol which are risk factors. The cholesterol treating compounds, AD risk should be reduced by induction of nitric oxide synthase; decrease of endothelin-1, this mechanism is independent with cholesterol. Some recent articles (Marx, 2001; Golde and Eckman, 2001a) well defined the relation between them, these author summarize mechanism behind this, these drugs gives priority to a-secretase and reduce the activity of b and g-secretases which inhibit formation of Ab. Furthermore, it has been expressed as inhibitors of acyl-coenzyme a cholesterol acetyltransferase and inhibitors of cholesterol esterification reduces the release of inhibit the Ab (Pettenati *et al.*, 2003).

Substances with a mitochondrial impact

Reducing Mitochondrial dysfunction by maintaining neuronal mitochondria which are responsible for maintenance of cell energy, generation of free radicals, activation of certain enzymes (caspases), use of oxygen in metabolism, synthesis of protein inhibitors play a role to reduce the risk factor of AD (Moreira *et al.*, 2005)³².

Hormones

Melatonin

Melatonin amount decrease with age it is a naturally produced hormone, which rapidly enters to brain through BBB and crosses all cell structures, it having antioxidant properties with mitochondrial support, reduce risk of tau tangles and decrease toxicity of β A some other factor like it enhance sleep and memory. Some studies shows its effects in AD patients³⁵. Some studies shows that treating patient with 6mg daily dose enhance mood and memory over 6 months with mild cognitive impairment. Another studies shows that daily dose 9mg given to patient with sleep disorder shows benefit effects over 23-35 months, but lower dose 3 mg daily dose of Melatonin shows no effects concluded by another studies³⁶.

Vitamins and minerals

Vitamin E

Vitamin E is considered as treatment of AD. Vitamin E (Alpha-tocopherol) a lipid soluble vitamin prevents cell from Ab by interacting to cell membrane and interrupts the chain reactions, antioxidant properties which prevents cell damage. Its antioxidant properties is not beneficial in Parkinson's disease it is not effective according to a research, while oxidation cause neuronal destruction (Doody *et al.*, 2001). Use of vitamin only delay the disability not prevent symptoms. some other evidence seen against the use of vitamin E due to its side effects (Doody *et al.*, 2001).(1) it is alternate to standard drugs used for AD, tacrine and donepezil because it is less expensive and less toxic another regarding its use in AD vitamin E is lower in AD patients².

Vitamin B

In elderly patients research shows that the reduced level of vitamin B12 in individual. Lower level of vitamin B12 and folate increase risk of cognitive decline. And B12, B6 and folate in combination lowers the level of homocysteine which is gradually high in AD patients but this combination had no effect on cognition because level of homocysteine levels related to aging not with cognition.

Vitamin A

Vitamin A is important for body because it is essential for learning, memory, and cognition. But in old age the vitamin A level reduced and its deficiencies also seen in AD patient. Multiple nutrients are deficient in AD, so there should be need to use multiple supplements (mixture of aALA, acetyl-L-carnitine, DHA, phosphatidylserine and glycerophosphocholine). Retinoic acid is a metabolic product of vitamin A is essential for reducing cell death and protect from β A.

Minerals lithium

Lithium is a found in many food products. Study in human subject shows that lithium enhance level of N-acetyl-aspartate which is responsible for protection of cell dysfunctions and cell death. It play an important role for improvement of neuroprotective protein such as bcl-2 in the hippocampus and frontal cortex parts of rat and

increased levels of phosphor late tau by inhibiting GSK-3 these factors which are responsible for cell death and β A plaques. Another *in vitro* study gives evidence about lithium inhibiting [Ca. sup. 2+] influx mediated by NMDA receptors.

Nutrients

Phosphatidylserine

Phosphatidylserine play an important role for increasing nerve growth factors. Phosphatidylserine having important show neurotransmission, mitochondria function, and cell metabolism properties. It has also been implicated in the enhancement of nerve growth factor. *In vitro* research shows that increases Ach and provides inhibiting β A and inflammation, shows neuroprotection action.

Alpha-lipoic acid

A fatty acid known as Alpha-lipoic acid (ALA), found in all cells and in some foods, produced naturally in the body. Antioxidant, reduces inflammation and increase ACH properties seen in ALA which are important for neuroprotective effects.

Omega-3 fatty acids

Omega-3 is a fatty acids which have many important roles for AD.

Acetyl L-Carnitine

It is small molecule derived amino acid L-carnitine derivative readily penetrates to BBB and enhance nerve growth, it essential for mitochondrial energy production transport of acetyl groups and fatty acids into mitochondria for energy production and clears toxic metabolites from mitochondria. It also enhance biosynthesis of A Chand it helps APP for preventing formation of amyloid plaque and preserves synaptic function.

Coenzyme Q10 (CoQ10; ubiquinone)/idebenone

Mitochondrial dysfunction activities including disruption of energy production, apoptosis deregulation, and altered calcium homeostasis are occurs in AD brain. For these reasons, mitochondria are viewed as promising the rapetictargets. CoQ10 reduced oxidative stress and taupathology in mice, and metabolized β A and inhibitedits formation *in vitro*. The reduction of β A found in a mouse model

was attributed to the antioxidant properties of CoQ10.

Diet

Recently reveal that by taking Mediterranean diet there was risk of lower AD. Maditerranean diet in which high consumption of fish, low to moderate consumption of saturated fatty acids, moderately high consumption of fish, low to moderately consumption of dairy products, low consumption of meat and poultry and moderate amount of ethanol intake. to A study signify that patients taking Mediterrane and ietlower risk of death in AD with possible dose-response effect³⁵.

Alternate therapies

Hormone-replacement therapy

Estrogen replacement

Estrogen-replacement therapy reduce risk of cognitive decline in postmenopausal women, woman which treated with estrogen therapy 50% risk of AD is reduced. It is believed that estrogens effective in terms of cholinergic, neurotropic and neuroprotective which may improve memory and cognitive². Recent study shows that woman taking estrogen improvement in cerebral metabolism. Studies demonstrated that estrogen alone not enhances cognition or function in patients, but by using its combination with progestin may beneficial for dementia and stroke³².

Stimulatory therapies

Cognitive functioning stimulated by physical exercise, cognitive training, and socialization. Some studies manifest that physical exercise beneficial for body and improve several factors such as enhance learning skills and memory, beneficial for vascular function, decrease inflammation, enhance metabolism, elevate mood, retard age-related memory loss, speed information processing, increase brain volume, aid hippocampal neurogenesis, improve synaptic plasticity, enhance brain derived neurotrophic factor, Increase dendritic spines, improve the glutamatergic system, decrease cell death enhance the blood supply to the brain and regulates chemicals such as insulin that are necessary for a healthy brain.

Recent hypothesis evince that music enhances steroid production which enhance neurogenesis, cell

repairs and improve neural plasticity. Cognitive training also beneficial for AD patients because it enhance cognition, supports for destruction of dysfunctional cells, enhance level of melatonin, improves neurogenesis and enhance plasticity. Socialization is another factor which having positive effects on AD patients because it reduce mood stress and depression and beneficial for cognitive functioning. Psychological factors also beneficial effects on because a positive attitude may stimulate patients to exercise, reduce depression and stress and engage in activities that are good for there health^{35,36}.

Herbal therapy

HuperzineA

It is widely used in China as Chinese folk medicine for many disease; it is Huperziaserrata extract which is a Chinese moss. Acetylcholinesterase found in different molecular forms such as G1, G2, G3 and G4. In human brain G4 found in large amount and G1 found in small amount. A study of in vitro and animal both shows that it increases ACh amount more than other Alzheimer's drug like tacrine, galantamine or donepezil also HupA penetrates BBB better than tacrine, donepezil, rivastigmine. HupA used for AD because it decrease β A-induction in hippocampus and cortex part of brain, inhibits glutamate toxicity, it protects neurons form cytotoxins, reduces oxidative damage by β A plaques, it protect neurons from apoptosis induced by β A and free radicals³⁵.

Curcumin

Curcuma longa (turmeric) is a source of curcumin which is diferuloylmethane found by extraction. Due to its anti-inflammatory and antioxidant properties it is used for many disease including AD. It having 10 neuroprotective activities such as anti-inflammatory, antioxidant, inhibition of β A formation, clearance of existing β A, and copper and iron chelation. It is widely used in India, that why there is lower incidence in India than other countries like US. Turmeric is a widely used spice in India its regular consumption is very beneficial, which may explain why India has a much lower incidence of AD than the United States. The dose of curcumin reduced by target to the colon^{35,37}.

Resveratrol

Resveratrol, found in a red wine, peanuts, and other plants is a polyphenol, It is used for AD patients because of its advantageous properties such as oxidative stress reduced, reduced inflammation, diminish β A, protects DNA, reduced cell death, and modulates various other systems that protect cells, reduces neurotoxicity, decrease degeneration of the hippocampus, and enhance learning skills. Resveratrol is quickly metabolized and excreted and its bioavailability is low similar to curcumin. Many studies demonstrate that use of red wine in moderate amount reduce risk of AD³⁵.

Herbal supplements

Ginkgobiloba

This herb is best known for AD, its symptoms and also for it enhances blood circulation. Ginkgo biloba have contains antioxidant and anti-inflammatory properties by which it useful for protection of neuron membranes, regulate neurotransmitters, prevent lipid from oxidation, retard cell degeneration reduce blood pressure and platelet aggregation. Its action show vasorelaxing activities. Its main constituent is ginkgolides, it having neuroprotective and cholinergic activities beneficial for AD. Study of a clinical trial by using placebo and a control group, shows that ginkgobiloba have similar activities as donepezil and tacrin. In united state it is used as a supplement in the United state and dispensed as a pharmaceutical in Europe, and also used in China as traditional Chinese medicine. Scientific evidence shows that it improves cognition decline in AD patients^{35,38}.

Panax ginseng

Panax Ginseng mainly cultivated in Northeastern Asia, from China and Korea it was used from ancient time. It is used since thousands of year for physical health and mental well-being. It contains steroid like compounds called ginsenosides. Ginsenoside Rg3 mainly play an important role in the reduction of β A1-42 by 84% *in vitro* and by 31% *in vivo*. Panax Ginseng have memory enhancing properties by scopolamine. Many studies reveals that it is play an important role in the enhancement psychomotor and cognitive performance, which is more useful for AD.

Withaniasomnifera

Withaniasomnifera is also known as ashwagandha or Indian ginseng. It is a nerve tonic. AD and other many disease are treated by Withania due to its properties such as anti-inflammatory, antioxidant, inhibition of β A, inhibition of calcium, inhibition of ACHE, reduction of cell death, prevent axon from damage, reduce neurite atrophy, restoring synapses and enhance memory and some other properties special with its chemical constituents such as withanolide-A preserves axons, whereas withanolides IV and VI preserve dendrites^{35,37}.

Other medicinal herbs

Herbs which may be used for AD have anti-inflammatory and antioxidant activities that may be used in the treatment. Anti inflammatory herbs reduce inflammation of the brain tissues in AD patients. In case of AD there is lower level of acetylcholine, it is a neurotransmitter which is important for reasoning and memory. Those compounds which increases the cholinergic system may useful in the AD, those herbs which inhibits inhibit Acetylcholinesterase (AChE) contain natural COX-2 inhibitors, with antioxidant and anti-inflammation. Some examples of these type of medicinal herbs are as follows; Salvia officinalis (Lamiaceae), Rosmarinusofficinalis (Lamiaceae), Bacopamonneria Wettst. (Scrophulariaceae), Melissa officinalis L. (Lamiaceae), Commiphorawhighitti (Burseraceae), Glycyrrhizaglabra (Fabaceae), Galanthusnivalis L. (Amaryllidaceae), Huperziaserrata (Lycopodiaceae), LipidiumMeyeniiWalp (Brassicaceae), Acoruscalamus L. (Araceae), Collinsoniacanadensis (Lamiaceae), Bertholettiaexcelsa (Lecythidaceae), Angelica archangelica L.(umbelliferae), Tinosporacordifolia (Menispermaceae), Urticadioica L. (Clusiaceae), Withaniasomnifera (Solanaceae), Magnolia officinalis (Magnoliaceae)³⁷.

Ayurveda therapy

Ayurveda is very usefull for age related cognitive decline either single drugs or formulations. Medhyarasayanas or other medhya drugs are

mentioned in one of them used for cognitive decline. Many drugs known as Medhyarasayanas which are beneficial for AD, for example Mandookparni (*Centellaasiatica*), Shankhapushpi (*Convolvulus pluricaulis*), Guduchi (*Tinosporacordifolia*) and Madhuyashti (*Glycyrrhizaglabra*) Brahmi (*Bacopamonneri*) and Jyotishmati (*Celastruspanniculatus*) are used in Ayurveda for treatment of AD. Ashwagandha (*Withaniasomenifera*) is widely used in Ayurveda, its scientific evidence shows that it is very beneficial for AD. Vidanga (*Embeliaribes*) shows increased grasping and retention power²³.

Challenges

Today AD patient population increases day by day thus development of medicines is important to prevent, delay, slow, or cure, but development is challenging due to several factors; such as;

There is lack of evidence and data, about AD progress has been made, but scientists still do not fully understand the underlying causes and mechanisms of the disease. This makes selection of viable targets for new medicines and use of new therapy is difficult.

There is lack of non-invasive biomarkers of disease activity and progression, which delays the diagnosis until patients become symptomatic. It takes long time and very expensive clinical trials. Diagnosis is challenging to evaluate³⁹.

Treating a brain disease is a challenging aspect because to treat AD or brain disorder the drug should cross the blood brain barrier, BBB is made of tight junction, it restrictes foreign particles to inter into BBB. Due to the presence of BBB an effective delivery to brain, development program cannot endure without equal efforts for discover and delivery of drug⁴⁰.

These challenges are complex in research and technology for success of drug development in Alzheimer's so there is lack of drug development, support and contributions by multiple stakeholders such as government, academia, industry³⁹.

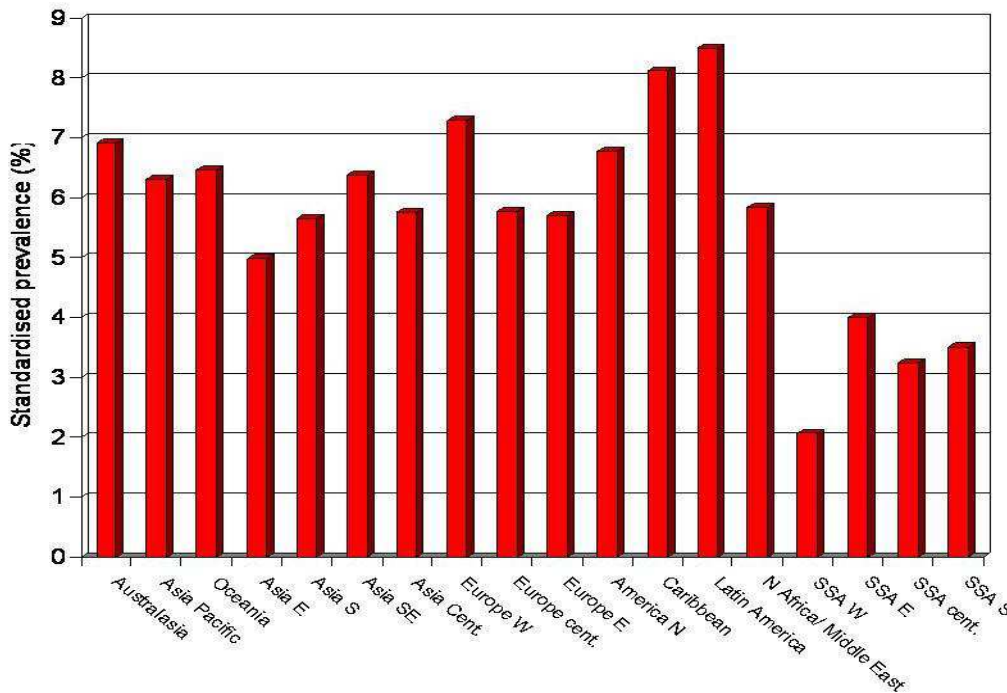


Figure No.1: Estimated prevalence of dementia for persons aged 60 and over, standardized to Western Europe population, by Global Burden of Disease region by WHO 2012

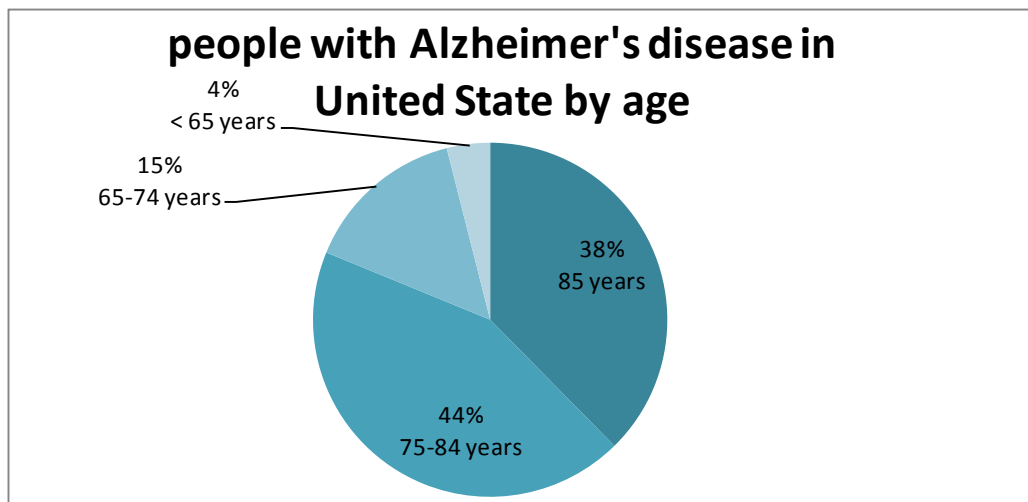


Figure No.2: people with Alzheimer’s disease in United state by age 2010 report, (Hebert et al)²

CONCLUSION

Few years back AD was not known by the society but as the time passes it emerge as a major CNS disorder and since then various researcher have made many important advances. It has expanded the knowledge of brain function. Over understanding about the AD helps us to overcome its treatment limitation. Many scientist are work out to find the

relationship between biological, environmental and genetical factors with AD. The combined effort of many scientific and clinical studies gives us an opportunities to manage as well as prevent this devastating social disease known as AD.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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