ALZHEIMER'S DISEASE: A REVIEW OF PATHOPHYSIOLOGY AND TYPES OF DEMENTIA

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ABSTRACT

Alzheimer's disease (AD) is one of the most prevalent neurodegenerative diseases, which is characterized by the impaired daily normal functions due to loss of neurons progressively in the brain. Accumulation of abnormal amyloid plaques and tau proteins are two pathological hallmarks in affected brain regions. The detailed mechanism of the pathogenesis of AD is still unclear; but a large body of evidence suggests that damaged mitochondria likely play fundamental roles in the pathogenesis of AD. It is believed that healthy mitochondria not only support normal neuronal activity by providing enough energy supply, but also guards neurons by minimizing mitochondrial related oxidative damage. In this review, we will summarize recent progress in the pathogenesis of AD and discuss mechanisms underlying in Alzheimer's disease, factors influencing Alzheimer's disease, Progression of AD, Types of Alzheimer's Dementias.

Keywords: Alzheimer's disease, mitochondrial dynamics, Axonal transport, Amyloid beta, Tau.

INTRODUCTION

Alzheimer's disease is a one of the progressive, irreversible neurodegenerative diseases of the brain. The neurodegenerative disease means that it worsening with time. Alzheimer's disease seems to begin 20 years or more before arise of the symptoms because of changes in the brain which are not noticeable to the affected person. After several years of the changes in brain individuals experience a certain noticeable symptoms such as memory loss, misplacing and language problems [1]. Symptoms will starts develop and progress with time because of the nerve cells (neurons) of the brain involved in thinking, learning and memory (cognitive function) have been damaged or destroyed. As the Alzheimer's disease progresses neurons in the other parts of the brain are also destroyed or damaged [2]. Those nerve cells (neurons) in the parts of brain that are helps a person to carry out some common basic bodily functions, such as walking, thinking and swallowing are also get affected. Some of the individuals will become a bed bound and require around the clock care. Alzheimer's disease is eventually leads to fatal of the patients [3]. Dementia is a term for a particular group of symptoms. Dementia referred as "group of condition characterized by impairment in memory loss and judgment of normal brain function". The some of the characteristic symptoms of the dementia are difficulties in speaking, recognizing, memorizing, problem solving and other thinking skills which will affect the person's ability to perform everyday activities.

Alzheimer's disease is one of the most common causes of dementia and it was estimated 60 to 80% of cases because of dementia. As per the recent studies of brain autopsy shows that more than the half of individuals with Dementia have Alzheimer's disease with changes in the brain. Difficulty in remembering the recent conversations, names, events as well as the depression are the early symptom of AD. Some common symptoms include confusion, impaired communication, poor judgment, disorientation, behavioral changes, walking, swallowing, difficulty in speaking and etc [4]. The pathologies of AD involve primarily accumulation of the protein fragment β-amyloid (plaques) outside the neurons in the brain and secondly twisted strands of the protein tau (tangles) inside neurons. These are the mainly responsible for the death of neurons and damage to the brain tissue [5].

Changes in brain associated with Alzheimer's disease

A healthy adult human brain has approximately 100 billion neurons with each and every neuron with long branching extensions. This extension of neuron will helps the individual neurons to form connections with other neurons. Such connections are called synapses in which information flows in tiny bursts of chemicals that are released by one neuron (pre-synapses) and detected by another neuron (post-synapses). The brain contains nearly 100 trillion synapses. Through which a signals can travel rapidly through the brain's neuronal circuits this helps in creating a cellular basis of memories, thoughts, sensations, emotions, movements and skills. The accumulation of protein fragments outside neurons called beta-amyloid plaques and the accumulation of an abnormal form of the tau protein inside neurons called tau tangles. These two are the main responsible for the changes associated with Alzheimer's disease in brain. Accumulations of large amount of beta-amyloid plaques called oligomers [6]. It is responsible for the damage and death of neurons (degeneration of neurons) by interfering in junction between two or more neurons were the communication takes place between neurons called synaptic cleft. Another protein called tau protein which will form tau tangles and disrupts the transport of nutrients and other essential molecules or essential nutrients inside neurons. This leads to the damage and death of neurons called neurofibrillary tangles. The complete sequence of events in Alzheimer's disease was unclear. But as per some of reported data the accumulations of beta-amyloid may begin before accumulations of abnormal tau protein and increasing beta-amyloid accumulation is associated with increases in accumulation of tau protein. The accumulation of beta-amyloid plaques and tau proteins are creating neurotoxin this result in immune system cells get activated in the brain called microglia. Microglia always tries to clear the toxic proteins as well as debris from the dying and dead cells. But microglia cells failed to clear accumulated toxic protein this results in formation of chronic inflammation. Further chronic inflammation may result in Atrophy or shrinkage of the brain occurs because of loss neuron cells in brain [7].

Dementia

Dementia is the loss of memory and other cognitive abilities serious enough to interfere with normal daily life.

TYPES OF DEMENTIA

Vascular dementia (VD): - It is the decline in thinking skills caused by the conditions that reduce blood flow and vital oxygen and nutrients to the brain & brain cells [8]. It is recognized as the second most common cause of dementia next to Alzheimer's disease. Various risk factors are involved in VD such as diabetes, obesity, hypertension, smoking, hyperlipidaemia and diet. One among various risk factors is diabetes were increased the risk of developing Alzheimer's dementia through the vascular disease and also through the deposition of various compounds that are derived from the hormone amylin in cerebral [9].

Mixed dementia: - It is a condition where characteristic abnormalities of more than one type of dementia occur simultaneously. Symptoms may vary depending upon of the regions of the brain get affected and changes in the brain occur which may be similar to those of Alzheimer's or another dementia [10].

Parkinson's disease: - It is also type dementia people with Parkinson's disease develop with impairment in reasoning and thinking. As brain changes gradually and they begin to affect 3 mental functions ability to pay attention, make sound judgments and steps needed to complete a task along with memory.

Dementia with Lewy bodies: - It is a type of progressive dementia associated with Alzheimer's and Parkinson's disease leads to the decline in reasoning, thinking and independent function due to the deposition of microscopic abnormal cells that damages the normal healthy brain cells [11,12].

Huntington's disease: - It is an autosomal dominant progressive inherited brain disease caused by the defect in a gene results in abnormal movements and difficulties in co-ordination. This results in changes in the central area of the brain and affects the mood, thinking skills and movement [13].

Creutzfeldt-Jakob disease: - It is degenerative brain disorder leads to the dementia. Creutzfeldt-Jakob disease is one of the common human forms of fatal brain disorders known as prion diseases. It has misfolded prion protein. These proteins will destroy the brain cells leads to the rapid decline in thinking, reasoning as well as involuntary muscle movements, confusion, difficulty walking and changes in mood [14].

Front-temporal dementia (FTD):- It is a group of disorders caused by progressive degeneration of cells in the brain's frontal lobes (the areas behind the forehead)

responsible for language, emotion, planning and motivation or in the temporal lobes (the regions behind the ears) [15].

Normal pressure hydrocephalus: - It is also a type of brain disorder in which excess amount of cerebrospinal fluid (CSF) get accumulates in the brain's ventricles results in thinking and reasoning problems with difficulty in walking and loss of bladder control [16].

Down syndrome dementia: - It is a type of dementia develops in people with extra genetic material one chromosome 21 among 23 human chromosomes. Individuals with Down syndrome they have a greater chance of developing dementia it is either the same or similar to Alzheimer's disease [17].

Korsakoff syndrome: - It is a memory disorder caused by the deficiency of the thiamine (Vitamin B-1). Korsakoff syndrome is commonly caused by the misuse of alcohol and alcoholic beverages, some other conditions can also cause the syndrome.

Posterior cortical atrophy (PCA):- It is the progressive degeneration of outermost layer of the brain (the cortex) located in the back of the head (posterior). The PCA is the unique disease or a variant form of Alzheimer's disease is still not known.

PATHOPHYSIOLOGY INVOLVED IN ALZHEIMER'S DISEASE

Alzheimer's disease is neurodegenerative disease and it is the sixth leading cause of death in the United States and mainly fifth leading cause of death among Americans at the age of 65 and older. As the Americans population increases with increases Alzheimer's dementia the burden of caring for that population is also increases [4].

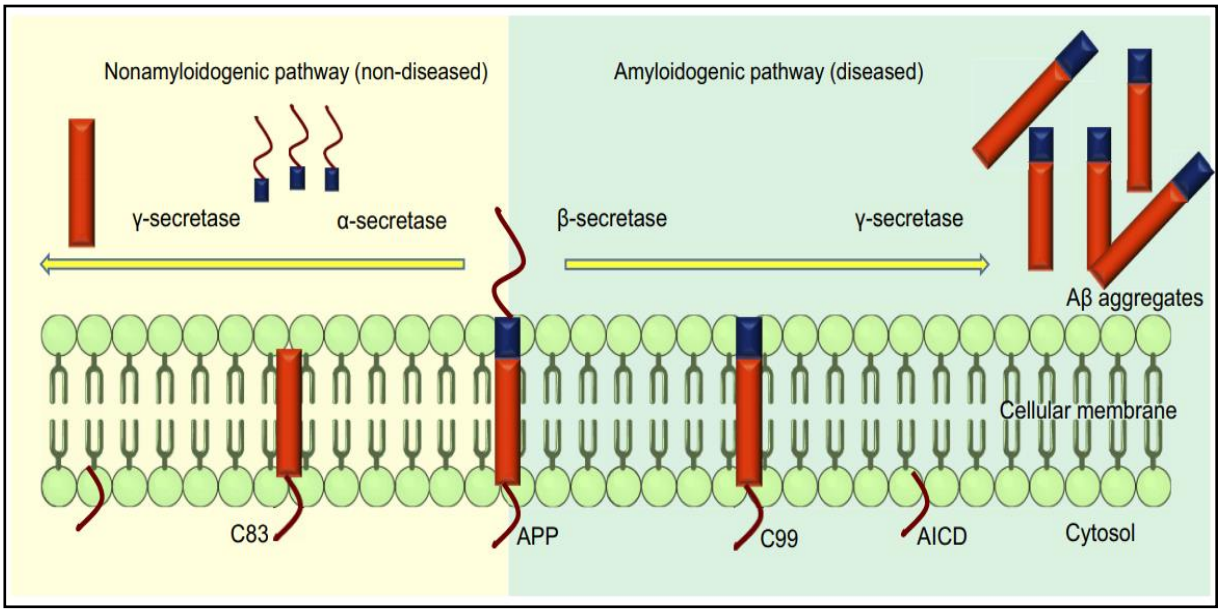
The globally the Alzheimer's disease is expected to accelerate from 2006 with 26.6 million cases to 2050 with 106.8 million cases. The Pathophysiology of Alzheimer's disease is attributed to a number of factors such as the cholinergic dysfunction, amyloidal toxicity, tau toxicity, oxidative stress and mitochondrial dysfunction [25].

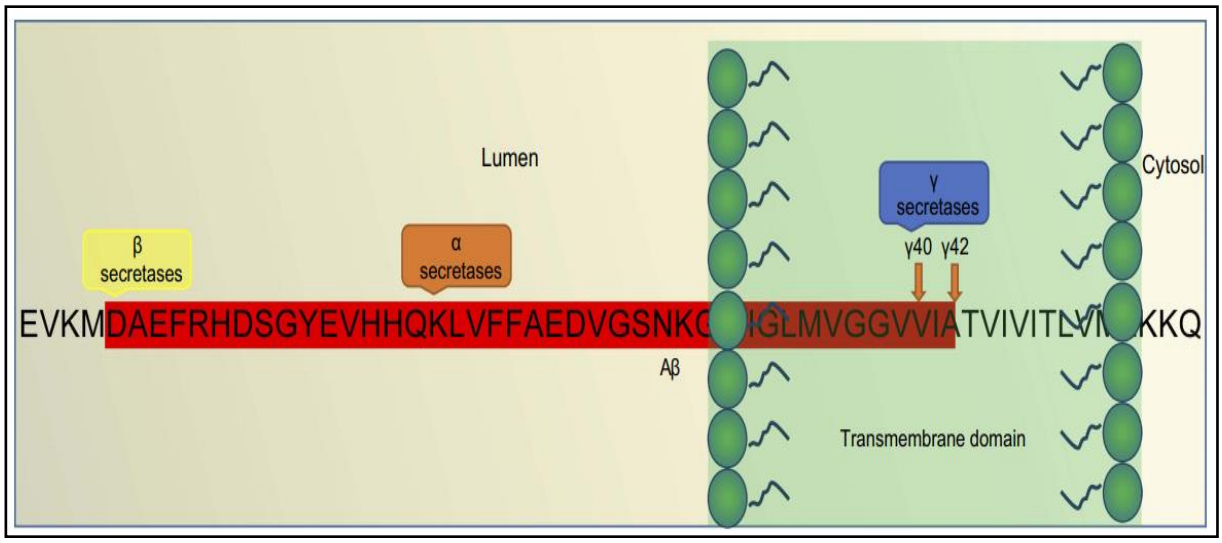
Amyloid precursor protein (APP) is belongs to the family associated with proteins that includes mammalian amyloid precursor like proteins (APLP1 and APLP2). Amyloid precursor protein (APP) is transmembrane protein with extracellular domains. In diseased state APP creates amyloidogenic fragments by cleavage through the enzymes. But the physiological functions of APP are not much clear. Some studies reveals that transfected cell lines show that APP moderates the cell survival, cell growth, cell

motility and along with neuritis outgrowth and functions. This may leads to the release of soluble ectodomains upon normal cleavage of APP by enzymes. APP encodes Type1 transmembrane glycoprotein, which is cleaved either via non-amyloidogenic pathway (normal state) or via an amyloidogenic pathway (diseased state). APP releases various peptides and polypeptides that arise due to alternative splicing, glycosylation, phosphorylation or complex proteolysis. APP comprises 770 amino acids in which Aβ includes 28 residues and 14 additional residues from the transmembrane domain of APP. At the cleavage site, α-secretase cleaves and secretes large soluble ectodomains (sAPP) into the medium and the C-terminal fragment C83 is retained in the membrane, which is further cleaved at residue 711 by γ-secretase and releasing soluble P3 peptide. In a diseased state, abnormal cleavage is takes by β-secretase releasing shortened sAPP and C-terminal fragment C99 is retained in the membrane and further it is cleaved by γ-secretase releasing insoluble Aβ peptides. Cleavage of both C83 and C99 by γ-secretase releases the APP intracellular domain into the cytoplasm, which is soluble and translocates to nuclei for further gene expression function [26].

Non-amyloidogenic pathway (Normal State)

The α-secretase enzyme will cleaves the Amyloid precursor protein (APP) at the residue 16–17 of the Aβ domain and it will yield soluble and non-pathogenic precursors. In neurons A Disintegrin and Metalloproteinases (ADAM10 and ADAM17) are considered the major α-secretases. The α-secretase and γ-secretase generates the small hydrophobic fragment p3, which is soluble and has a role in normal synaptic signaling, but the exact function is still to be clarified. It has been reported that cell surface APP may get endocytosed as well, resulting in endosomal production of Aβ, which may leads to extracellular release and aggregation of Aβ. The α-secretase processing and releases the large soluble ectodomain sAPP, which is not neurotoxin to the brain. The presence of sAPP helps to associates with normal synaptic signaling, adequate synaptic plasticity, learning, memory, emotional behavior and also neuronal survival. The sequential processing and releases the APP into the intracellular domain which will further translocates into nuclei and facilitates nuclear signaling and gene-expression and regulation of gene pathway [26].





Amyloidogenic pathway (Diseased State)

In Amyloidogenic pathway, APP is cleaved differently in the diseased state by the enzymes. Aβ is released from APP through the sequential cleavages by BACE-1 (membrane spanning aspartyl protease) with its active site situated in lumen and γ-secretase (intramembrane aspartyl protease) made up of four proteins: - presenilin, nicastrin, anterior pharynx defective 1 and Psen2 which are complexed

together. This complex will contribute to the activity of γ-secretase which will produce insoluble and neurotoxin Aβ fragments. It removes majority of the extracellular portion of the protein with leaving the C-terminal of the APP, which is further cleaved at the C-terminus of Aβ, resulting in the formation of the Aβ monomers or Aβ oligomers that further polymerize leads to the formation of aggregated plaques. There are two main types of Aβ polymers that have direct role in plaque formation and induced neurotoxicity: - Aβ40 and Aβ42. Aβ40 is abundant and less neurotoxin than Aβ42, Aβ42 less abundant, highly insoluble, severely neurotoxin and chances of more aggregation and it acts as a toxic building fraction of Aβ assembly. Aβ40/Aβ42 aggregation results in blocked ion channels, altered calcium homeostasis, increased mitochondrial oxidative stress, diminished energy metabolism and glucose regulation, it is responsible for the deterioration of neuronal health and finally to neuronal cell death [26].

Hyperphosphorylation of tau

Alzheimer's disease is characterized by the presence of Neurofibrillary tangles (NFTs). NFTs are because of hyperphosphorylation of the tau protein associated with microtubule. Microtubules are the microscopic hollow tubes made up of special kind of tau proteins helps in holding of alpha and beta tubulin to from microtubule as a part of cell's cytoskeleton. NFTs are the fragments of paired and helically wound protein filaments in the cytoplasm of neurons cell. The tau protein has a microtubule binding domain and co-assembles with tubulin to form matured and stable microtubules. The tau protein has ability of stabilizing microtubules and forming interconnecting bridges between other microtubules to form a proper uniform stable network of microtubules and hold them together. The tau protein comes to contact with the kinases that are released due to the abundance of Aβ in the external environment tau gets hyperphosphorylated. The hyperphosphorylation of tau leads to oligomerization of tau. This leads to microtubules gets unstable due to dissociation of tau protein followed by tubulin subunits, these convert into big chunks of tau filaments which further aggregate to form NFTs. These NFTs are straight, fibrillary and highly insoluble patches in the neuronal cytoplasm and it processes leading to abnormal loss of communication between neurons and signal processing and which will finally leads to apoptosis of neuron. Some recent study

reported that soluble Aβ will control the cleavage and phosphorylation of tau protein for generation NFTs. The phosphorylation of tau is regulated by several kinases including Glycogen Synthase kinase 3 (GSK3β) and cyclin-dependent Kinase 5 (CDK5) which is activated by extracellular Aβ. And also GSK3β and CDK5 are primarily responsible kinases for the hyperphosphorylation tau. Some other kinases like Protein Kinase C, Protein Kinase A, ERK2, a serine/threonine Kinase, Caspase 3 and Caspase 9 which may be activated by Aβ [26].

FACTORS INFLUENCING ALZHEIMER'S DISEASE

Age

Age is one of the greatest risk factor of Alzheimer's disease. The prevalence of occurring of Alzheimer's disease were increasing dramatically with age 3% of people at a age of 65-74, 17% of people at age of 75-84, 32% of people at age of 85 or older [27,28].

Genetic Risks of AD

The apolipoprotein-e4 (APOE-e4) gene is the important gene with the strongest impact on risk of late onset of Alzheimer's disease. APOE-e4 will provide the information for a protein that involves in the transport of cholesterol in the bloodstream. Each and Everyone will inherit any one of allele among these three forms (alleles) of the APOE gene e2, e3 or e4 from each parent which is result in six possible APOE pairs: e2/e2, e2/e3, e2/e4, e3/e3, e3/e4 and e4/e4. Having the e4 form of APOE has chance of increase one's risk of developing Alzheimer's compared with having the e3 form, but it does not conforms that an individual will develop Alzheimer's disease. Having the e2 form there is decrease of one's risk developing AD compared with having the e3 form. Those who inherit one copy of the e4 form they have about three times the risk of developing AD compared with those with two copies of the e3 form while those who inherit two copies of the e4 form they have chance of 8 to 12 fold risk developing AD. Those with the e4 form are more likely to have beta-amyloid accumulation and Alzheimer's dementia at a younger age than those with the e2 or e3 forms of the APOE gene. A Meta analysis along with 20+ published papers describe the frequency of the e4 form among people in the United States who had been diagnosed with Alzheimer's found that 56% had one copy of the APOE-e4 gene and 11% had two copies of the APOE-e4 gene. Another study

found that among 1,770 diagnosed individuals from 26 Alzheimer's disease Centers across the United States 65% had at least one copy of the APOE-e4 gene. A small percentage of Alzheimer's cases an estimated of 1% chance of develop AD due to the mutations in any of the three specific genes [4].

Family history

A family history is not only a factor to develop Alzheimer's disease in individual. The individual who have first degree relative with Alzheimer's dementia are more likely Alzheimer's disease than that of who don't have first degree of relative with Alzheimer's dementia [29,30]. The individuals with more than one first degree of relative with Alzheimer's are higher risk of developing AD [31].

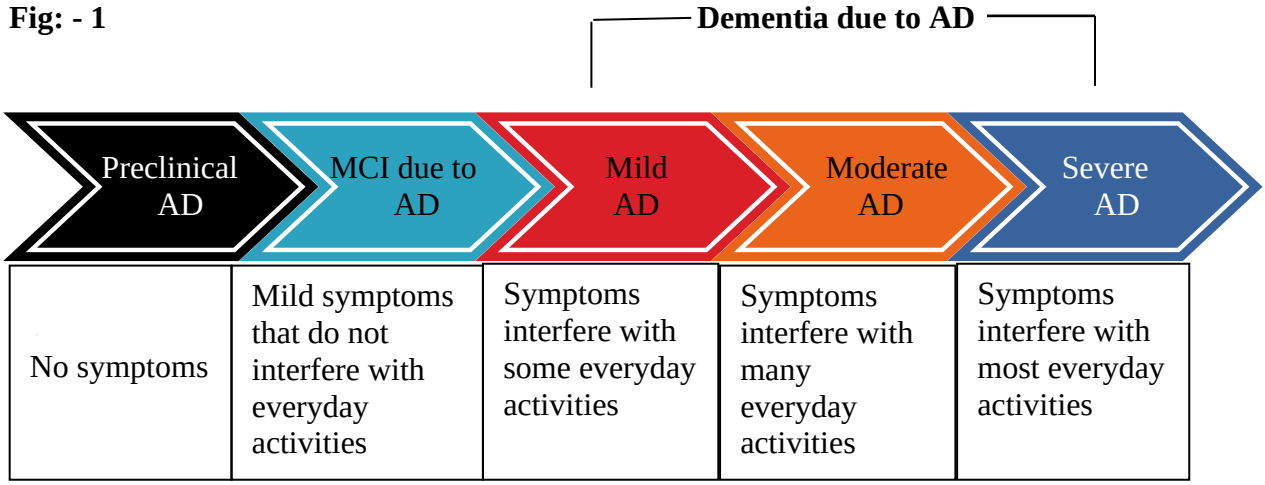
Down syndrome

In Down syndrome an individual is born with three copies of chromosome mainly chromosome number 21 (called Trisomy 21) instead of two. Peoples with Down syndrome have chance of increased the risk of developing Alzheimer's disease and this is believed to be related to the trisomy 21. Chromosome 21 includes the gene that encodes for the production of amyloid precursor protein (APP). The people with Alzheimer's have amyloid beta fragments that will accumulate into Aβ plaques. Having an extra copy of chromosome 21 may lead to overproduction of Aβ fragments in the brain.

People with the Down syndrome develop Alzheimer's disease at earlier age than people without Down syndrome. At the age of 40 most of the people with Down syndrome they have significantly higher the level of Aβ plaques and tau tangles in their brains. As mainly with adults as the age increases person with Down syndrome will exhibit symptoms of Alzheimer's. According to the National Down Syndrome Society (NDSS), about 30% of people with Down syndrome they have Alzheimer's dementia at 50s. About 50% of people with Down syndrome they have Alzheimer's dementia at 60s [4].

Progression of Alzheimer's disease (AD):

Fig: - 1



The progression of Alzheimer's disease results in the changes in the brain and it is unnoticeable to the affected person that cause a problems with memory, thinking and physical disability it is called the Alzheimer's disease progression. In this progression of Alzheimer's disease there are three main phases of Alzheimer's Disease: **Preclinical Alzheimer's disease**, **Mild cognitive impairment (MCI)** due to Alzheimer's disease and **Dementia** due to Alzheimer's disease (Fig:-1) [18,19,20]. The **Alzheimer's dementia phase** is further divided into different stages called **mild, moderate and severe**. As we know that progression of AD starts with preclinical Alzheimer's and followed by it will ends with severe Alzheimer's dementia. The length of each phase of the progression is mainly influenced by age, genetics, gender and some of other environmental factors [21].

❖ **Preclinical Alzheimer's disease:**

In preclinical phase where individuals have considerable changes in brain which will indicate the early signs of Alzheimer's disease. But they have not yet developed the symptoms of loss of thinking skills, recognizing and memory.

❖ **Mild cognitive impairment (MCI)**

People with MCI due to AD they have evidence of biomarker in changing brain (abnormal level of β-amyloid, tau protein) of Alzheimer's patients and problems associated with memory and thinking skills.

But one analysis reveals that after 2 years of follow-up mainly 15% of individuals who are older than 65 years of age had developed dementia [22]. Whereas other study was found that 32% of individuals developed with MCI of Alzheimer's dementia within 5 years of follow up [23]. One more study among individuals found that 38% developed dementia in MCI when it was tracked it for 5 years or longer [24]. In which some individuals with MCI reverts to normal cognition or it remains stable. Identifying the individuals with MCI is a major goal of current research that is likely to develop Alzheimer's or other dementia.

❖ **Dementia due to Alzheimer's disease:**

Dementia due to Alzheimer's disease is characterized by certain noticeable signs and symptoms such as memory, thinking, recognizing or behavioral symptoms which will impair a person's ability to function normal in day today life, along with evidence of Alzheimer's related brain changes. Individuals with Alzheimer's dementia will experience certain multiple symptoms that will change over a period of years. These symptoms reveal extent of degree of damage to nerve cells (neuron) in different parts of the brain. The symptom of dementia advance from mild to moderate to severe differs from person to person.

- **Mild Alzheimer's dementia**

In the mild stage of Alzheimer's dementia most of the peoples are able to function independently in many areas but are still likely to require assistance with some of the activities to maximize the independence and remain safe. They are still able to drive, work and participate in many of activities and favorite activities.

- **Moderate Alzheimer's dementia**

In the moderate stage of Alzheimer's dementia it is the longest stage where individuals may have experience difficulties in communicating and performing his daily routine tasks including activities of daily living.

- **Severe Alzheimer's dementia**

In severe stage of Alzheimer's dementia where individuals compulsory needs help in daily activities around the clock care. The effects of Alzheimer's disease on individual's physical health will clearly visible in this stage. The damage of the part of individual's brain that is mainly involved in movement and recognizing results in the individuals becomes a bed-bound. Being

bed bound of individuals makes them vulnerable to conditions including blood clots, skin infections and sepsis which will triggers the body's inflammation that may result in failure of organ. Even damage to the areas of the brain that control swallowing makes difficult to eat and drink. This will result in the individuals swallowing food into the trachea (windpipe) instead of the esophagus (food pipe). This result in food particles may deposit in the lungs and may cause lung infection. These types of infection were referred as aspiration pneumonia and it may contribute to cause of death among many individuals with Alzheimer's [4].

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