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Research Article

Recent Trends on Epidemiology, Histopathology, Clinical Diagnosis and Treatment Measures of Alzheimer's Disease

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Abstract: This article describes that Alzheimer's disease is one of the most significant neurodegenerative diseases. It is a grave public brain disorder. Many people, around the world, do not only suffer from this disease but also die due to it. This article deals with the genetic and environmental risk factors responsible for Alzheimer's disease. Alzheimer's disease occurs due to the deposition of misfolded amyloid proteins. Since the time when Alois Alzheimer discovered it, intensive research is being done on the clinical symptoms and possible treatments of the disease. Multiple anti amyloid β drugs had been proposed long time ago but have only limited effects. Tau based drugs have been recommended and have significant effects on the patients. Yet, many strategic therapeutic approaches are still to be explored for the complete cure of Alzheimer's disease. Further researches and approaches had undergone various experiments to conquer this disorder.

Keywords: Alzheimer's disease, epidemiology, histopathology, neurodegenerative disorder, amyloid β drugs, glial cells.

INTRODUCTION

Mutations in the nucleotide sequences of DNA lead to the synthesis of conformationally abnormal proteins. These misfolded proteins can aggregate and pave the way for diseases. There is either the loss of normal protein functioning or there is toxic gain of their function. Since, almost all disorders are the result of defective enzymes (proteins). Neurodegenerative diseases also involve the deposition of abnormal protein in different portions of the brain (neurons as well as glial cells).

Neurodegenerative diseases are characterized by the selective loss of neurons. There are several types of it. Some of them are depicted in figure No: 1.

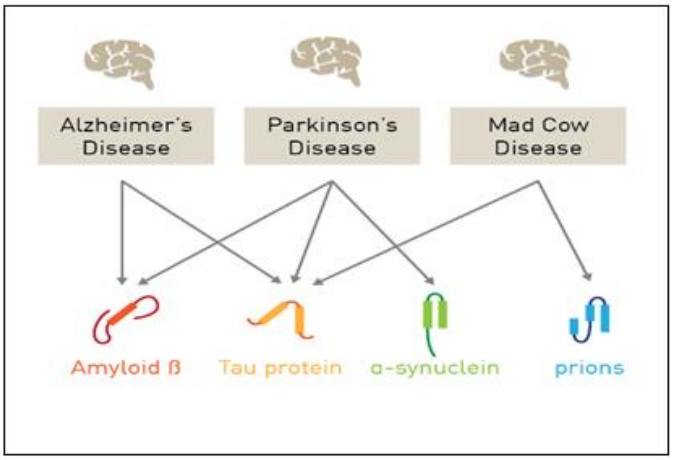

Fig-1: Several types of neurodegenerative diseases with their defected proteins

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Alzheimer's disease is a progressive a neurodegenerative disease and is also the consequence of defected protein accumulation in brain. In its general term, Alzheimer's disease is a late life intellectual failure that has attained high life anticipation. This disease manifested in language, memory and behavior is basically an aggressive form of dementia. It includes three groups of symptoms. Alzheimer's disease can persist for decades. Alzheimer's disease progresses slowly. The three stages of this disease possess their own symptoms and challenges (Figure No: explains three stages of Alzheimer's disease).

The symptoms and severity of the disease are unique to each patient. The symptoms advances from mild stage memory loss to severe dementia as depicted in figure No: 2.

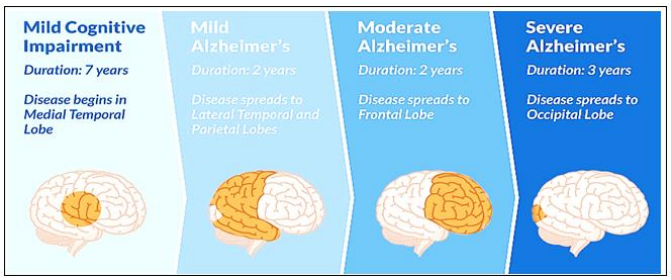

Fig-2: stages of Alzheimer's disease and affected lobes

Now, several drugs exist that can stop the advancement of neurodegeneration process in Alzheimer's disease. The treatment of this disease has symptomatic nature [1].

Brief Historical Perspective

In 1901, Dr. Alois Alzheimer, German neuropathologist as well as physiatrist, got the credit of uncovering a state of dementia, which was later termed as Alzheimer's disease, for the first time [2]. Max Knoll and Ernst Ruska, in 1931, invented the Electron microscope that has magnification of about 1 million times. This made the detailed study of brain tissues possible. In 1968, cognitive measurement scales were developed and with the help of which researchers measured the volume of destroyed brain tissues as well as estimated the impairment. 1974 led to the establishment of National Institute on Aging that is still supporting the Alzheimer's Research. From 1983, November was declared as First National Alzheimer's Disease Month. The main purpose of this action was to give awareness about the disease to the people. In 1984, National Institute on aging started to provide funds to Alzheimer's Disease Centers. 1993 was the year when foods and Drugs Association (FDA) approved the first drug for Alzheimer's Disease i.e. Cognex [3]. It targets the symptoms of the dementia and memory loss. In 1994, the genetic study of the Alzheimer's disease began in order to detect the risk genes of the disease. In 2013 UK, an effort was done to fight Alzheimer's disease on international level by the G8 Dementia Summit.

Epidemiology

Alzheimer's disease is a critical public health disorder [2]. In USA, it is considered as 6th leading cause of death. During last 15 years, it has been acknowledged that heart diseases have been decreased up to 11% while an increase of 123% in Alzheimer's disease has been observed. About 72% of the dementia cases involve Alzheimer's disease as its principal cause [4]. The global incidence of this disease at present is about 24 million. And this number is supposed to be doubled after every two decades. This disease is common in developing countries.

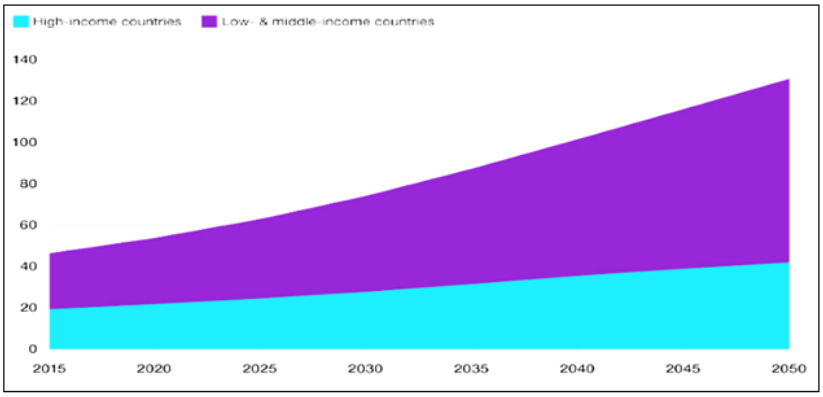

Fig-3: world Alzheimer Report

If Alzheimer's disease runs in family, it will increase the risk of developing the disease [5]. People suffering from familial Alzheimer's disease have autosomal dominant mutation in amyloid precursor protein gene or in presenilin gene present on chromosome 21 and 1 or 14 respectively. Alzheimer's disease being a multifactorial disorder is influenced by several risk factors such as aging. The early onset of Alzheimer's disease, before the age of 65 years, is the consequence of rare genetic mutation [6]. About 95% of all the cases involve late onset of the disease i.e. at age of 65 or more. The risk of disease increases 2 times every 5 years after 65 years of age [7, 8]. Females are mostly affected by this disease [9].

CAUSES

At an early stage of disease, the only noticeable symptoms in Alzheimer's patients is increasing amnesia, unusual trouble in organizing thoughts and recalling things, mild confusion etc. But as the time passes, the memory loss increases especially the recent memories are lost. The symptoms vary from person to person and depend on age. The causes of Alzheimer's disease are described by three hypotheses.

Amyloid Hypothesis

When misfolded amyloid proteins abnormally get deposited in the brain tissues, the condition is known as Amyloidosis. In these amyloid deposits, reduced tissues are noticed. Amyloid β Precursor protein (abbreviated as APP) is a membrane protein that is proteolyzed to make Aβ that forms plaques of amyloid in brain of Alzheimer's patients [10]. According to this hypothesis, Alzheimer's disease is due to presence of Aβ deposits in brain tissues [11]. This hypothesis had compelling evidences. Because the mutations in the gene encoding the APP was found to be responsible for familial Alzheimer's disease. If β secretase proteolyzes the APP through amyloidogenic pathway then APPsβ and C99 are produced. But if a non-amyloid genic pathway is followed then Appam C83 is the product.

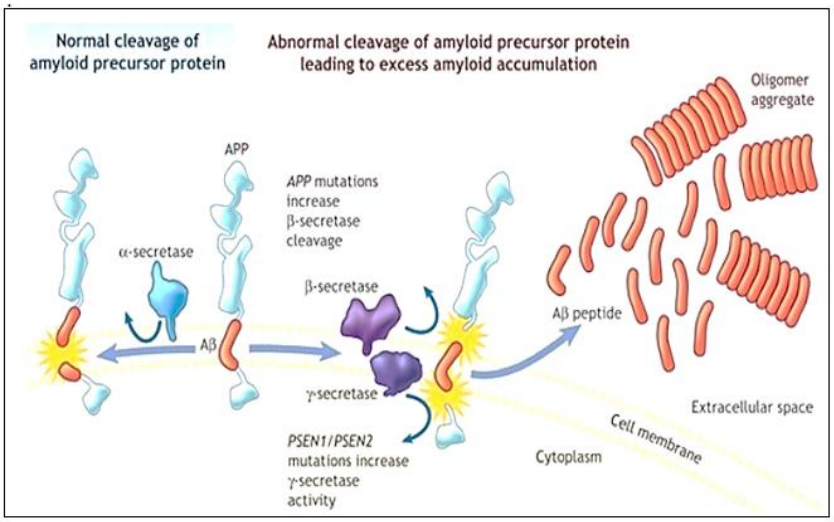

Fig-4: Schematic representation of Abnormal APP cleavage

Cholinergic Hypothesis

This hypothesis revolves around the fact that acetyl choline (ACh) has significant role in memory and learning process. It was supposed that the decrease in non-cognitive and cognitive functions is associated with the reduction in cholinergic nerve cells and neurotransmitters. But no causal link between them was established [12]. Secondly, the utilization of cholinesterase inhibitors does not have any substantial impact on Alzheimer's disease sufferers that shows the involvement of other processes in the advancement of disease.

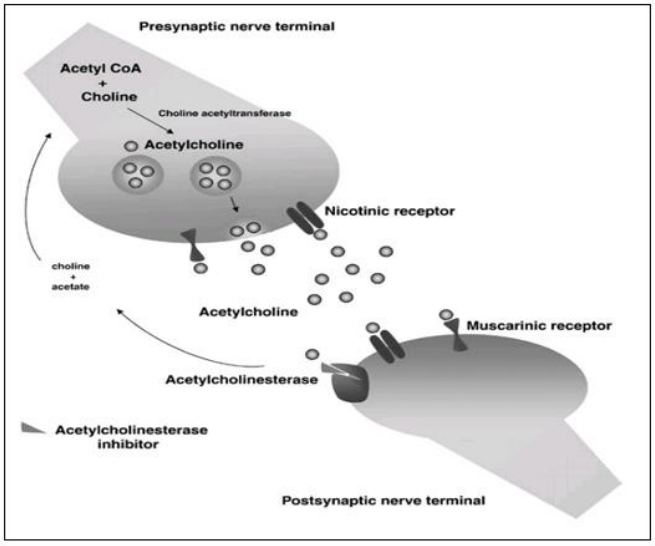

Fig-5: Schematic diagram of Cholinergic Hypothesis

Tau Hypothesis

This hypothesis says that neurofibrillary tangles are associated with Alzheimer's disease. Tau protein is basically bound to microtubules and its increased phosphorylation results in the increase in free tau proteins. The overall result is the loss of functioning microtubules. Paired helical fragments (PHFs) tend to make neurofibrillary tangles (NFT) [13]. And these Paired helical fragments have free tau proteins as their subunits. The impaired microtubules affect the axonal transport of protein. And finally causes death of nerve cells which is one of the characteristics of Alzheimer's disease [14].

Environmental Factors

Certain environmental and genetic factors are responsible for any disease. Alzheimer's disease is generally considered to be the product of genetic mutations, but several toxic and infectious factors are also responsible for this (as depicted in figure No: 6). Different types of infectious agents can attack the tissues of brain. The pathologic changes in the brain regions, such as the deposition of amyloid plague, are directly linked with slow viruses.

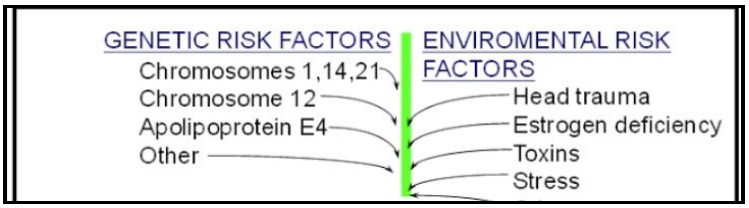

Fig-6: Several Genetic and Environmental risk factors for Alzheimer's disease

Normal aging

The normal aging is a weakly understood process. This process can be accomplished by fine and gross anatomical changes or any neurologic, neurophysiological and neurochemical changes. But such changes are not helpful in determining the abnormal changes in brain. The brain analysis of the two 80 years old persons (one person is normal while other is suffering with Alzheimer's disease) shows that their brain condition is almost identical. Several years before the onset and diagnosis of disease, impairment in several cerebral domains can be observed [15]. As the age increases the Alzheimer's disease get worsens.

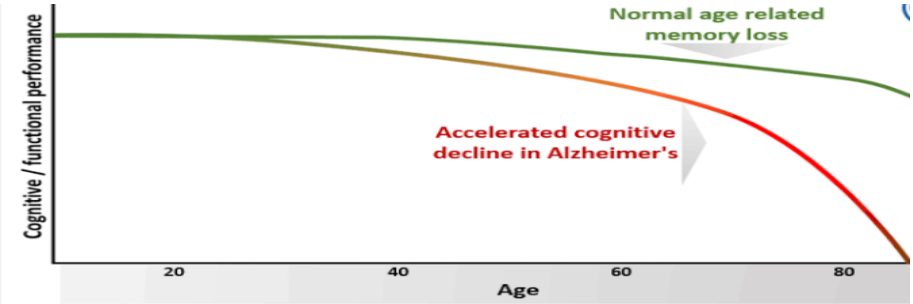

Fig-7: Relationship between Normal aging and Alzheimer's Disease

The diagnostic process of Alzheimer's disease will continue to be difficult until we get an improved understanding of usual aging process. We can understand the abnormal changes only if we are able to get better data about normal psychological, neurological and biological mechanisms. Changes in the functions of brain regions that are linked with cognition, perception and emotions accompany the aging process [16].

Molecular genetics

In 1984, the location of gene responsible for Alzheimer's disease was predicted to be on chromosome 21. Glenner and Wong described the amino acid sequence of key constituent of β-amyloid which they referred to as "Amyloid β Protein''. Their analysis was based on the cerebrovascular amyloid derived from the Alzheimer's patients [17]. A link between the apolipoprotein E (Apo E) and onset of Alzheimer's disease is present [18]. ApoE4 is found to develop and aggravate the disease. This gene is present on chromosome 19 and is responsible for late onset of disease. While ApoE2 has opposite effects i.e. it tends to protect from disease. As mentioned above, the early onset of this disease is due to the chromosomal mutations. And chromosomes that undergo mutations are 1, 14 and 21 [19]. The risk for first degree relative of this disease is higher 10-40 % as compared to unrelated persons.

Co-existing health Issues

Several other disorders in the Alzheimer's patients can aggravate the Alzheimer's disease. As a result, the patients suffering from other health problems can also go through the Alzheimer's disease. Several problems that co-exist with Alzheimer's disease are depicted in the figure below.

When Alzheimer's disease gets worse, it enhances the risk of falling. And this can result in broken bones and head trauma. Some people also suffer from depression whose symptoms involve mood swings, insomnia, less communication with people and lack of concentration. Since the clinical symptoms of depression and Alzheimer's disease are similar, it is sometimes difficult to predict the disease from which the person is going through. In Alzheimer's patients, a solid connection between brain and heart health has been observed. Moreover, high cholesterol level and high blood pressure also triggers the onset of Alzheimer's disease. This occurs due to the detriment of blood vessels that result in the drastic death of brain tissues due to less blood flow towards them. Type II diabetes can also enhance the risk of developing Alzheimer's disease [19].

Diagnostic Approaches

Diagnosis of Alzheimer's disease at an early stage involves the psychometric and neuropsychological tests. Moreover, blood test, cerebrospinal fluid, electroencephalogram (ECG), functional, structural and molecular neuroimaging are performed [20]. The diagnosis of Alzheimer's disease follows a particular criterion as presented below:

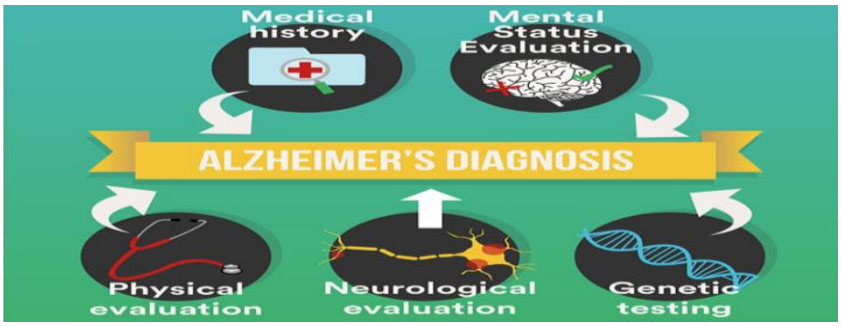

Fig-8: Diagnostic criteria1 of Alzheimer's Disease

The recent neuropathologic criteria are based on the estimation of Alzheimer's disease neuropathologic variation [21]. The comprehensive diagnosis of the disease needs genetic studies as complementary test [22].

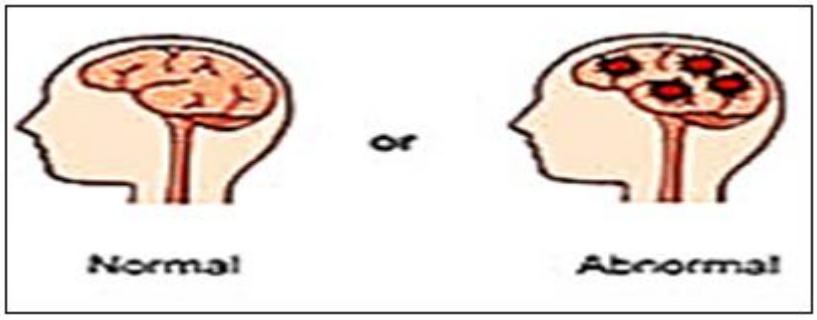

Fig-9: Conventional detection techniques vs. recent techniques

Clinical diagnosis of Alzheimer's disease follows a logical sequence:

- **The patient history includes the information from the informant**
- **Cognitive function test: for the assessment of patient's mental state.**
- **Physical examinations that emphasizes on the neurological and vascular signs augmented with investigations [19].**

In most of the cases, the bi-step process of dementia assessment is employed. In the first step, the dementia syndrome is distinguished from all other disorders (e.g. depression, cognitive impairment etc.) that imitate them. Second most important step is the diagnosis of the subtype of the dementia syndrome since this will help in the determining the type of possible and available treatment.

Detection Techniques

A powerful understanding of the nervous system disorders and neuroanatomy is made possible by the tremendous development of techniques for non-invasive imaging of brain. Neuroimaging has been acknowledged as an auspicious and ever-expanding field of research that has enabled the only observes the damaged areas of brain but also diagnose the type of brain disorder. The preliminary tests for the diagnosis are as follows:

PET-Positron Emission Tomography

PET scan acts as an effective aid in Alzheimer's disease Diagnosis. PET scan provides better information of the cell loss in brain as compared to other neuroimaging techniques. The reason for this can be that it indicates blood flow and metabolic changes in the measurements of whole brain [23,24]. PET sometimes in combination with some other less cumbersome devices can be used as non-invasive way of quantifying the oxygen and glucose utilization in the brain tissues. PET requires large labor and more facilities and the accessibility of local cyclotron. Due to these reasons, it is used less. Sometimes, PET uses 18F-Fluoro-deoxy glucose (FDG-PET) as radioactive tracer and measure degree of the regional brain metabolism. The early signs and symptoms of Alzheimer's disease can be detected by using FDG-PET technique. A recent development is the introduction of in vivo PET based amyloid imaging. It uses particular radioactive ligand that binds with amyloid plaques in the brain tissues.

MRI-Magnetic Resonance Imaging

In 1977, MRI techniques were first used to diagnose the injuries and illness by creating images of the body that can be two- or three-dimensional. The most significant part of the MRI system is super conducting magnet. A magnetic field, produced by this component, is large and stable. And different parts of body are scanned with help of magnets. In Alzheimer's patients, cellular death in brain is detected with this technique Sometimes the atrophy in the hippocampus is observed even before the appearance of the symptoms of Alzheimer's disease [25].

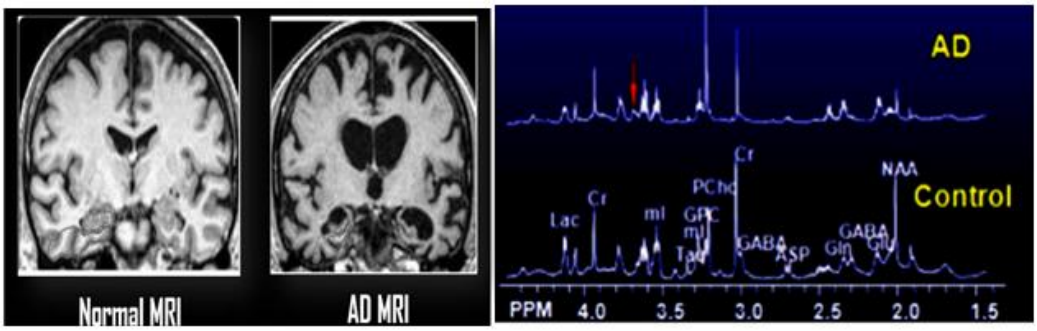

Fig-10: Brain NMR results of (normal) control group vs. Alzheimer's patient

Nuclear Magnetic Resonance (NMR)

With the help of this technique, the high-resolution imaging of brain morphology can be done without exposing the Alzheimer's patient to the harmful ionizing rays. It has been acknowledged as most valuable approach among the neuroimaging technique for diagnosing the Alzheimer's disease [16]. The main reason for this is their versatility, adaptability and flexibility. It can not only provide accurate measurements of Cerebrospinal fluid (CSF) volume but also distinguish between white and gray matter. Moreover, it can detect cell protein changes, brain tissue destruction and small infracts.

Computed Tomography (CT-SCAN)

This technique is abbreviated as CT-SCAN technique. It is the most available of neuroradiological devices. It Alzheimer's patents, it is used to assess the integrity of brain tissues and to visualize cerebral atrophy. In this technique, cross-sectional images of the brain regions are taken and then each single scan is integrated with the help of computer. These scans are then incorporated into a single detailed image. Sometime a contrast dye can be used to differentiate between similar tissues. Doctors can observe the density of brain tissues in Alzheimer's patients with help of this technique. Cortical atrophy, extracellular matrix variations and enlarged cerebral ventricles can be analyzed by more sophisticated CT. In addition to the diagnosis of Alzheimer's disease, the CT scan can also be used periodically to determine the progression of disease.

Single photon Emission Computed Tomography

This technique, unlike PET scan, does not require a cyclotron as a source of positron. It is more readily usable alternative to the PET scan and relatively economical method. But usage of these techniques in the diagnosis of Alzheimer's diseases is in its start [16].

Neuropathology

Alzheimer disease is an advanced neurodegenerative disorder of brain that results in a remarkable interruption of normal brain function and structure. AD, at cellular level, is considered as progressive loss of pyramidal cells of cortical neurons, which are responsible of higher cognitive functions [26]. Early in the disease course, synaptic dysfunction occurs which eventually disturbs the communication within neuron cells that is responsible for memory and some other cognitive functions [27]. In AD disease, degeneration of neuronal cells begins in medial temporal lobe especially in cortex and hippocampus which is further spread to parietal areas, throughout the temporal cortex, frontal cortex and finally in the remaining neo-cortex. Multiple components of limbic system also have pronounced effects such as hippocampal formation. This pattern of neuro-degeneration has adverse effects on both neocortical and limbic regions and the patient with AD shows cognitive impairment, and usually experience emotional, psychiatric and personality disorders and impaired ability to perform daily life activities [2].

Neuronal damage in AD is basically due to storage of abnormal protein in neurons both in the inside and outside regions. Theses pathological hallmark lesions of AD is recognized as "Plaques and tangles". Deposition of abnormal protein begins in cerebral cortex and further spread in stereotypical pattern along neuronal pathways that facilitate the cognitive functions including memory [26]. Normally, soluble amyloid-beta protein (Ab) is released by cells after the cleavage of cell surface receptor: APP, throughout the life. But in AD, precipitation of Ab into bets sheets occurs as a result of abnormal cleavage of APP and eventually forms "senile plaques"

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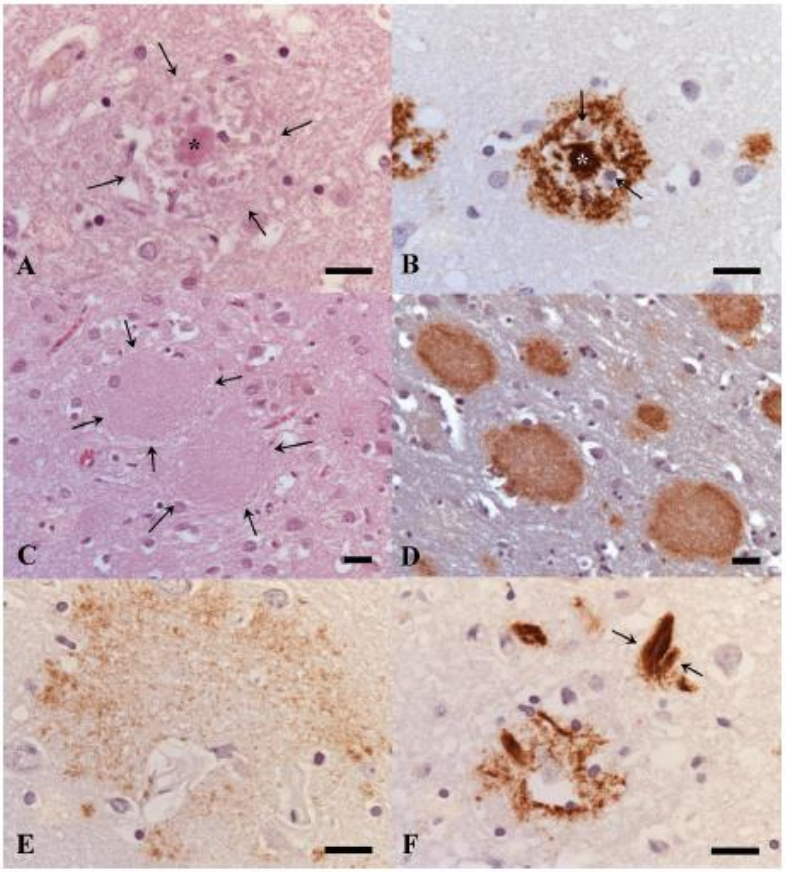

Fig-21: Aβ accumulation

A) Senile plaque aspects are shown B) immune-stained Aβ is shown at the center while macrophages are present at surroundings of core. C) cotton wool plaques are shown D) Immune-staining of cotton wool plaques E) A diffuse deposit of Aβ F) immunostained deposit with anti- Aβ antibody [28].

Inflammatory response that helps to clear the amyloid aggregates is caused by microglia and astrocytes. This inflammation also likely to cause the deterioration of adjacent neurons and their axons and dendrites [8]. Normally, tau protein, characterized as a microtubule stabilizing protein, has function in intracellular transport of axons and vesicles. However, abnormal hyper-phosphorylated form of tau protein forms intracellular aggregates called as "Neurofibrillary tangles" (NFT). NFT may interfere normal neuronal functioning and survival by disrupting proper axonal transport, and leads neurons to dies. Amyloid generation and accumulation in cerebral cortex is the initial pathological process in AD, prior to solid onset of disease by 10-20 years. A recent research proposes that earlier generation of NFT occurs in brainstem instead of formation in the medial temporal lobe and first amyloid plaques appear in the neo-cortex [29]. Figure below shows the β-amyloid, inflammation, NTF and atrophy are the hallmark of AD disease which appears at different stages of life. Expertise suggests better cure of AD by diagnosing the disease at correct time span.

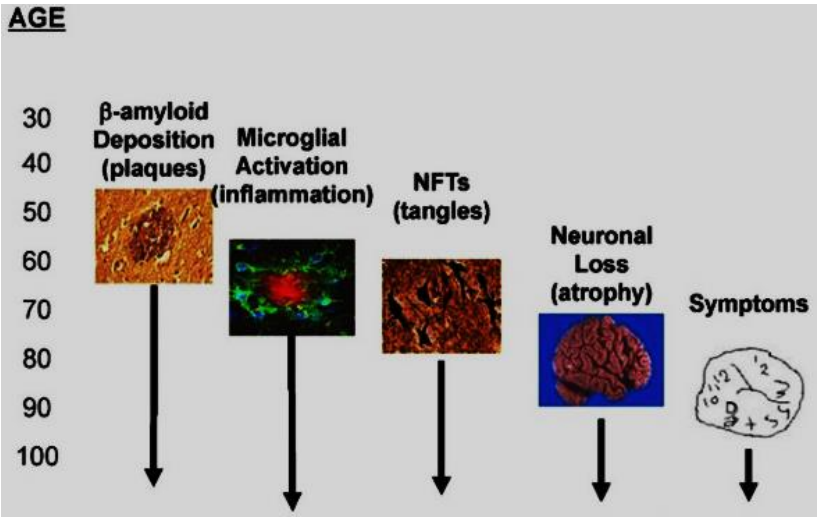

Fig-22: Pathological processes in AD

Treatment

Complete cure for Alzheimer disease is not possible yet. However, drug therapy for this disease is still to be explored. Available medications for the cure of probable Alzheimer disease aids to control the disease symptoms. But it is not possible to reverse or slowdown of progression of disease [6]. Mainly two types of drugs used to cure this disease that is acetyl-cholinesterase inhibitors and the other one is N-methyl D-aspartate antagonists. Working principle is different for both drugs.

Cholinesterase inhibitors (CI)

Lower level of a chemical named acetylcholine is present in brain of the patient with AD disease. This chemical functions to sends messages between nerve cells. Basically, memory disturbances are treated by the use of CI inhibitors by increasing the acetylcholine availability level in synaptic neurotransmission. For the basic treatment of AD disease in mild to moderate form, currently there are three CIs are being used: galantamine, donepezil and rivas-tigmine [11]. Galantamine inhibits Ach along-with butyryl-chlolinesterase while rivas-tigmine and donepezil both are selective inhibitors. However, donepezil and rivas-tigmine exhibited no substantial effect on the ADLs, cognitive functions and behavior. Overall, all three medications, showed similar benefits [30]. It is not possible yet to slowdown the disease progression by using CIs, however, they seem to have effects for significant period of time. It is observed that long term treatment with donepezil exhibits no significant loss for up-to two years, in a randomized double-blind trials [31]. Moreover, increased dose of given CIs shows some added benefits. A 48 week study is conducted to determine the effects and safety of rivas-tigmine drug of increased level of dose, in a randomized double blind trials. And reduced ADLs destruction level along with improvement in Alzheimer Disease Assessment Scale-cognitive-subscale (ADAS-cog) is significantly observed in treated patients with higher dose [32]. Side effects by the use of CIs drags to minimal and are related to gastrointestinal symptoms like nausea, diarrhea and vomiting. Various guidelines on the uses and efficacy have been issued by The National Institute for Health and Care Excellence (NICE). In addition, they analyzed the commercial benefits of drugs along with provided treatment.

NMDA Receptor Antagonists

Another FDA approved non-competitive drug Memantine is used for the treatment of moderate to severe AD. Glutamate induced excite-toxicity is reduced by the modulation of NMDA receptors. Treatment results in reduced deterioration, shows positive effects on cognitive functions including less agitation in patients, needs reduced help from caregivers and behavioral improvements. Memantime treatment also highlighted the improved behavioral and psychological symptoms regarding dementia. (BPSD)

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[33]. In case of severe Alzheimer disease, memantine is recommended by NICE guidance as a part of NHS care. Memantine is recommended to patients with moderate AD disease because they cannot use cholinesterase inhibitor drugs due to possible side effects.

BPSD is a major problem in Alzheimer disease and ultimately a problematic burden on caregivers. Mamantime and CIs are used to minimize these symptoms up-to certain extent but as the patient continue to deteriorate, the impact become less effective. Depression is a common occurrence in entire course of disease. To counter this problem, antidepressant including selective serotonin reuptake inhibitors (SSRI), serotonergic along with noradrenergic inhibitors and tricyclic agents are used. Depression increases in patients who discontinued the use of antidepressants thus, shows the beneficial signs of antidepressants [34]. Psychosis and agitation are treated by the use of typical antipsychotics including quetiapine, olanzapine and risperidone in AD. However, remarkable decline in cognitive functions appear to occur with the routine administration of such drugs, so, the use of antipsychotic drugs is somehow controversial [35].

Disease modifying treatments

Symptomatic treatment is proven helpful as amyloid hypothesis shows that overexpressed APP cleavage results in Aβ generation and deposition forms the basis of Alzheimer's disease. So, anti-amyloid therapies have been considered and resulted in increased clearance of Aβ, reduced production of Aβ and blockage of Aβ aggregation into amyloid plaques [10]. Immunotherapy has been considered for the treatment because it aims in clearing of Aβ peptide which has effects on cognitive functions either directly or indirectly [36]. Aβ production is decreased in various ways mainly by directing the amyloid genic and non-amyloid genic pathways. B and secretases with β and Y-secretase processing strive for APP and thus resulted in amyloid deposition and production of soluble APPSC respectively. Aβ production and deposition is reduced by inhibiting β and Y-secretase, while at the same time activating the Y-secretase action, as a whole. It is believed that AD is caused by synergistic effects of genetics, environmental factors and lifestyle that ultimately lead to damage of brain cells. In the following table, drug dosage formulations and indications are shown. CIs drugs are used in mild to moderate form and donepezil is also used for severe form. In 2014 combination of drugs is experimented to treat severe form of A.D in addition of memantine [37].

Current research on therapeutic approaches and future perspectives

Current researches are being conducted on various mechanisms for early diagnosis as well as to minimize the occurrence and progression of disease. New mechanismwhich are considered to be involved in pathophysiology of AD such as mitochondrial dysfunction, inflammation, oxidative stress, caspase, lack of neutrophin and sirtuins, has undergone in recent researches. Intensive researches and experimentation will provide effective and innovative therapeutic approaches for the treatment of disease in the very near future. There are three steps on AD course modifying research. First, manage modifiable risk factors by selecting high risk population and providing primary prevention. Second step involves the diagnosis of AD at preclinical phase by exploring various techniques such as CSF investigation, neuroimaging techniques and genetic studies [38]. Third, determine the disease modifying molecules. Researches basically focused on inhibition of extracellular amyloid plaque deposition and intracellular inhibition of tau related neurofibrillary tangles accumulation.

Table-2: Amyloid directed management approaches of AD

Amyloid based therapies	Processing steps	References
Anti-amyloid agents	Amyloid Cascade Hypothesis capture some aspects of disease process, which shows • **Mutation in genes of amyloid metabolism forms the basis of AD** • **Deposited amyloid plaques has toxic effects**	[39]
I. Secratase modulators	Decrease Aβ production by • **Modulating enzyme that breakdown amyloid precursor protein** • **Stimulating α- Secretase** • **Inhibiting β and γ- secretases** • **B-Secretase inhibitors also show some failure, but still researches continue.**	[40]
II. Amyloid anti-aggregants	Prevent amyloid aggregation in precipitated form by	[41]

	• **Develop anti-Aβ aggregating agent that is tramiprosate, colotrinin, clioquinol.** • **Studies shows conflicting results but there are ongoing researches.**	
III. Immunotherapy	Attenuation of Aβ plaques in brain by • **Induce a humoral immune response to fibrillary Aβ42** • **Passive administration of anti-Aβ antibodies.**	[42]

Tau related immunotherapy targets to reduce the generation of intracellular neurofibrillary plaques or tangles. Reduced Hyper-phosphorylation of tau proteins and APP reduction is accompanied by lithium. But its toxicity effects in older patients limits its use. It is observed in recent clinical trials that reduced amyloid process has no significant effects on cognitive abilities. Other methods aim on NFT and as a result synapses loss and neuronal cell death occurs. That's why, tau related immunotherapies (active and passive) are well growing with prominence effects [43]. Various researches are being conducted on compound like monoamine modulators, nicotine acetylcholine receptors and AMPA based receptors but the outcomes are still in debate. NGF treatment is performed by inserting NGF expressing surgically that copy the endogenous formation of NGF. Xaliproden aims to stimulate the endogenous formation of NGF as well as increases the hippocampal choline aceyl-transferase production. There are ongoing phase III studies evaluating the possible effects of this approach [44]. Another peptide cerebrolysin has a neutrotrophic activity and is responsible for Aβ deposition. It is observed by experimental studies that cerebrolysin facilitates cognitive functions as well as daily life activities. Clinical examination of cerebrolysin is still to be continuing [45]. NGF and NGF based drugs has neuro-restorative properties and many innovative research is expected to continue. Lastly, there is lot of research on disease modifying behavioral approaches, management tactics, and social supports as well as on the significance of primary prevention methods.

CONCLUSION

Early diagnosis of the neuro-degeneration is vital in Alzheimer's disease as it delivers a chance for early treatment that may facilitate to slowdown the progression of disease. Detection of AD is primarily based on clinical considerations and neuro-psychological tests. However, exact diagnosis of AD is accompanied by exploring well growing genetic, chemical and neuroimaging biomarkers. Recent treatment of AD is performed by using cholinesterase inhibitors and memantine. Moreover, additional social guidelines and further researches will grant some surplus information to clinical practice. Multiple approaches are under investigation and few have significant effects in AD patients. Anyhow, various researches still need to conquer different tussles like regulations, legal aspects and the requirement of in vivo and bio-distribution studies of different therapeutic theories, before AD progression speeds up.

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