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ALZHEIMER'S DISEASE: PAST, PRESENT AND FUTURE

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Abstract:Alzheimer's disease (AD) is one the oldest neurodegenerative disorder that impairs memory and cognitive judgment, described in ancient texts over many centuries ago and in year 1907; 51-year-old woman was the first case which was reported by Dr. Aloysius in modern world. However, our knowledge is too little and it is characterized by the formation of neurofibrillary tangles (intracellular) and amyloidal protein (extracellular), leading to senile plaques formation. Currently, available treatments only minimize the impact and decelerate the progression, providing only relief not cure. From the last two decades, researchers are extensively investigating the various pathophysiological events but, still we are unable to understand the clear mechanism. In this review, we discuss the various pathophysiological mechanisms underlying the Alzheimer's disease and various future aspects and novel predictions to treat dementia and associated consequences.

Index Terms **- Alzheimer's disease, neurofibrillary, amyloidal protein, dementia.**

I. INTRODUCTION

Alzheimer's disease is a neurodegenerative brain disorder of unknown etiology and most recognized type of dementia that generally starts in late middle age or in old age which bring about dynamic memory loss, hindered thinking, confusion and changes in individual character and state of mind. There is excessive loss of brain neurons particularly in the cerebral cortex and presence of neurofibriallry tangles and plaques containing beta amyloid cells. AD was first characterized in 1906 by Dr. Alois Alzheimer, a German doctor, Alzheimer had a patient named August D, who suffered from mental illness. When she died, Alzheimer used the staining technique to look at her brain microscopically. He finds the neuritic plaques outside, and around her brain. Inside the cells were twisted strands of fiber, or called as neurofibrillary tangles**.** ***(Kumar 2014)***

According to World Health Organization approximately 44 million people live with dementia worldwide at present and it is believed that these numbers will double by the end of 2050. AD ranks as the leading cause of death in US and United Kingdom. In the coming years the largest increase in dementia occurrence is predicted in the developing countries, which show displays patterns of increasing cardiovascular disease, hypertension and diabetes. While the extensive majority of AD takes place on an apparently irregular basis, mutation in 3 genes amyloid precursor protein(APP),presenillin(PSEN) and presenillin2(PSEN2). ***(Lane 2017)***

The majority (more than 95 %) of the AD cases belong to sporadic variety of the disease which is a multi-factorial disorder in which both genetic predisposition and environmental factors contribute to the genesis of the disease. The most distinguished neuropathological hallmarks are extra neuronal senile plaques and intraneuronal neurofibrillary tangles (NFTs). The subsequent loss of neuronal synapses and neuronal death leads to decreases in acetylcholine and other neurotransmitters. ***(Chakrabarti et al: 2015)***

The diagnosis of AD is done by evaluating the location, distribution, and abundance of characteristic brain lesions. The neuroimaging techniques are promising and capable of both quantifying AD related cerebral atrophy and detecting amyloid beta peptide, phosphorylated tau inside the brain. Autopsy or biopsy neuropathologic is to be considering the gold standard for the diagnosis of AD. ***(Thakur et al: 2019)***

According to world Alzheimer report the top nations who are affected by Alzheimer's disease include, Finland, Kuwait,Turkey,Saudi Arabia, United kingdom,Tunisia,Libya,United States, Syria and Lebanon and those with lowest rate include India, Cambodia ,Georgia and Singapore.

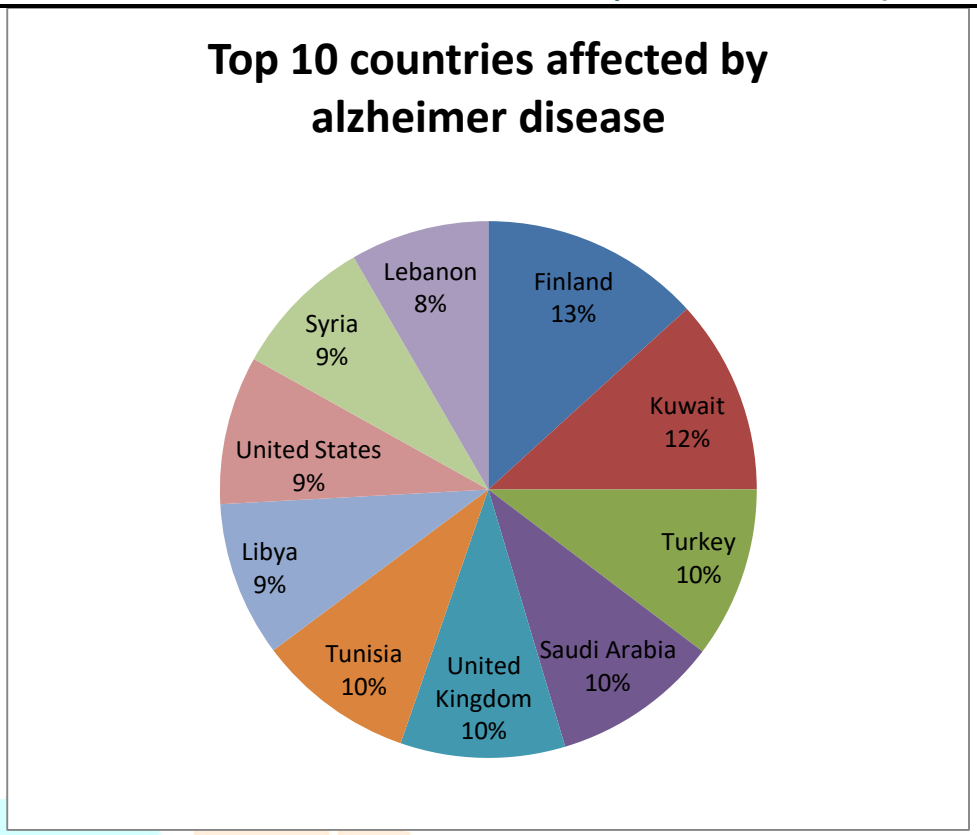

Figure 1. Top 10 Countries Affected by Alzheimer's disease.

II. PATHOPHYSIOLOGY

At present, the leading theory for the cause of AD depends on the amyloid cascade hypothesis and Tau hypothesis.

2.1 Amyloid Hypothesis

According to amyloid cascade hypothesis the progressive accumulation of amyloid beta in the brain leads to the formation of senile plaques and causes oxidative stress. Amyloid beta are insoluble small peptides, which are formed by the cleavage of the amyloid precursor protein by secretase enzyme (alpha- secretase) and (beta- secratase) which can lead to the abnormal production of amyloid beta. Amyloid beta can then trigger a complex cascade events leading to the neuronal cell death or loss of neuronal synapses. These effects contribute to the clinical symptoms of dementia. ***(Oboudiyat et al: 2013)***

2.2 Tau Hypothesis

Tau is a protein which is generally present in the neurons whose function is to stabilize the microtubules into cell cytoskeleton. Hyperphosphorylation takes place which will remove the hyperphosphorylated tau into neurofibrillary tangles (NFT) and the neurofibrialary tangles will gather inside the nerve cells.These tangles then abnormally interact with cellular proteins; as a result, the microtubules will disintegrate leading to cell death. This leads to Alzheimer's disease. ***(Briggs et al: 2016)*** Figure 2 shows the pathophysiology of Alzheimer's disease.

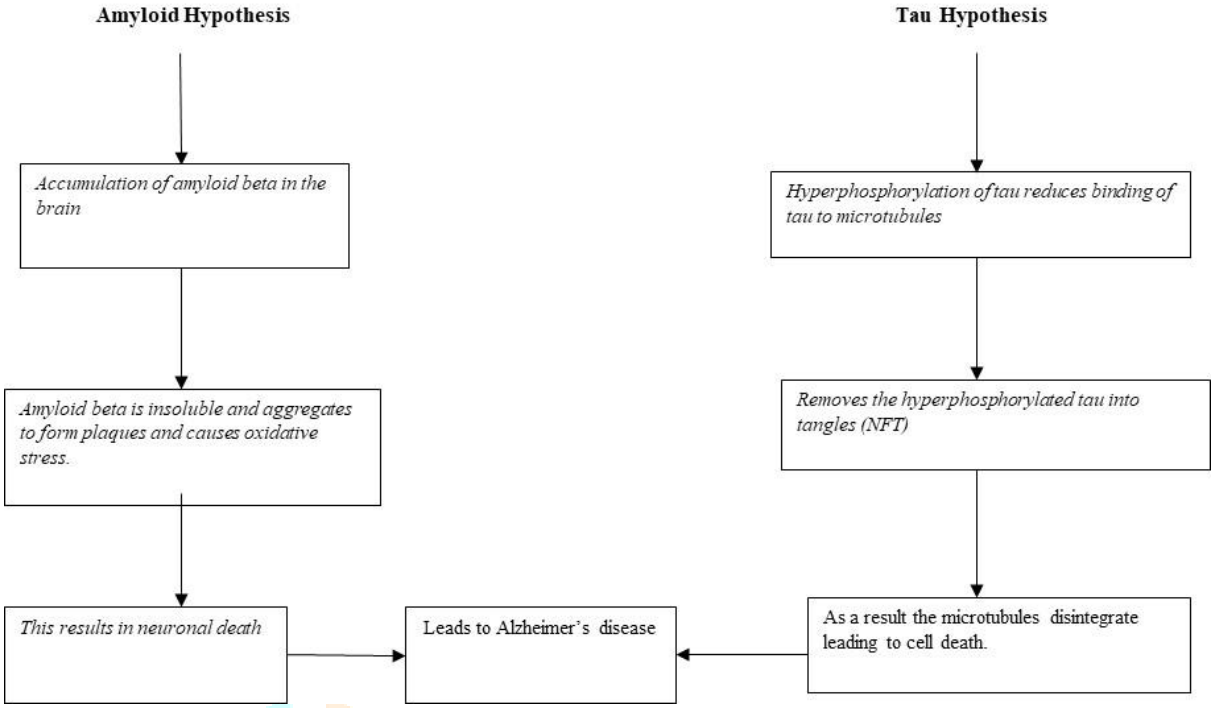

Figure 2. Flow diagram of AD Pathophysiology

Causes

The advancement of Alzheimer's disease is identified due to two anomalous proteins in the brain called as amyloid beta and tau,and creates proteins clump known as tangles and plaques these proteins clumps causes neuron death by blocking nerve cell functions. The exact cause of AD is unidentified. For the vast majority of people, Alzheimer disease is caused by hereditary and natural factor that influence the brain over time. ***(DA et al: 2014)***

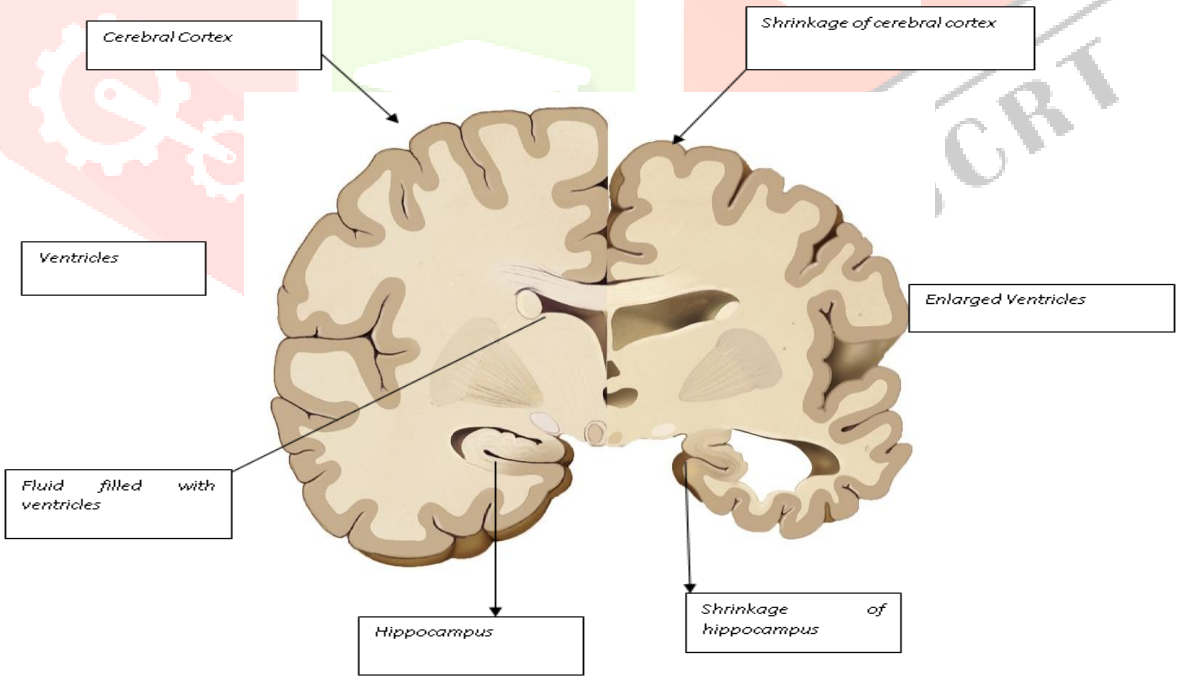

Figure 3. Brain changes in Alzheimer's disease (Healthy Brain VS Alzheimer's disease)

What happens to the brain?

The cortex shrinks and damaged the areas involved in thinking, planning and remembering. Shrinkage is particularly severe in the hippocampus, an area of the cortex that plays a key role in formation of memories. In ventricles the cerebrospinal fluid filled spaces within the brain grow large.

III. STAGES OF ALZHEIMER'S DISEASE

Alzheimer disease is classified into four stages; they are:

- Pre- clinical stage
- Mild (early) stage
- Moderate (middle-stage)
- Severe (late-stage)

3.1 In Preclinical stage include all the unseen changes in the brain, consisting of plaque accumulation.

3.2 In Mild stage the patients start forgetting and difficulty in recalling new names and conversations and also involve changes in personality such as decreased motivation or becoming easily upset or anxious.

3.3 In Moderate stage the patients become more forgetful, increasing dependence on others for daily cares, requiring help in decision making and include behaviour changes such as repeated questioning and hallucinations (seeing or hearing things which are not there).

3.4 The last stage is the severe this is the longest stage in AD the patient is unaware of time and place and inability to identify close family members. As the disease advances patient require an increase level of care for daily activities. ***(Khan et al: 2016)***

IV. RISK FACTOR

- Age
  Developing age is the well-known risk factor for Alzheimer disease. As you become older the chances of building up Alzheimer disease increases.

- Poor sleep designs
  Research has shown that poor sleep patterns, such as difficulty falling asleep or staying asleep are associated with an increased risk of Alzheimer's disease

- Past Head Injury
  Individuals who've had an extreme head injury have a larger possibility of Alzheimer's disease

- Genetics
  The possibility of progressing Alzheimer's is increases if one of the family members is suffering from the disease. A difference of the gene APOE e4, increases the chances of Alzheimer's disease, but not everyone with this similarity of the gene develop the disease.

- Lifestyle and other risk factors
  Sedentary lifestyle can increases the chances of AD and is defined as "sitting for a long time and not moving much" which causes significant impact on health and other factors such as obesity, hypertension, smoking cause AD.***(Eratne et al:2018)***

V. PHARMACOLOGICAL TREATMENT

5.1 Acetyl cholinesterase inhibitors

Presently, there are four AChi are available for treatment of AD. These are donepezil, galantamine, rivastigimine and tacrine. Tacrine is not given now because it shows liver toxicity. These are given for the patients who are in middle or late stage of AD. These drugs increase the cholinergic neurotransmission by inhibiting the cholinesterase enzyme. ***(Chu et al: 2012)***

5.2 Mechanism of action of Acetylcholinestrase

Ach inhibit the cholinesterase enzyme into acetate and choline which will break the neurotransmitter Ach. Cholinesterase enzyme are of 2 types i.e. acetylcholinestrase and butrylcholinestrase.donepezil, galantamine and rivastigime will inhibit the Ach Enzyme and rivastigime will also inhibit the butrylcholinestrase leading to increase the level of acetylcholine and thus improves brain function. ***(Kumar 2014)***

5.3 NMDA receptor antagonist (N-Methyl-D-Aspartate Receptor Antagonist)

Mematine is an NMDA receptor and act as an antagonist of NMDA receptor indicated for moderate to severe Alzheimer's disease. Mematine block the overexcited NMDA receptor relieve the Mg ions and block the entry of Ca which causes excite toxicity due to glutamate (an excitatory neurotransmitter in brain) which will act on NMDA receptors which result in neuronal death. ***(Malve 2016)***
Mematine can protect neurons by reducing the tau phosphorylation with a decline in glycogen synthase activity***. (Precoma et al: 2016).***

New drugs under development for Alzheimer's disease:

Table 5.1: Drugs under development ***(Cummings et al: 2019)***

Drug name	**Indication**	**Company**	**Development Status**
Aducanumab	Alzheimer's disease	Biogen	Phase 3
AC-1204	Mild to Moderate Alzheimer's disease	Accera, Broomfield	Phase III
ANAVEX2-73	Alzheimer's disease	Anavex Life Sciences	Phase 3
BPN14770	Alzheimer's disease	Tetra Therapeutics	Phase 2
Crenezumab	Alzheimer's disease	Roche/Genentech	Phase 3
AstroStem	Regenerate neurons	Nature Cell Co	Phase 2
Vorinostat	Neuroprotective	German Center for Neurodegenerative Diseases, University Hospital, Bonn, University of Gottingen	Phase 1
3K3A-APC	Alzheimer's disease	University of Southern California (USC) in Los Angeles	Pre-clinical phase
NPT088	Clear amyloid	Proclara Biosciences, Alzheimer's Association	Phase 1
LY3002813	Alzheimer's disease	Eli Lilly	Phase 1
ABvac40	Alzheimer's disease	Araclon Biotech	Phase 2

Current Treatment

Currently there are 3 drugs approved by the US FDA for the treatment of Alzheimer's disease namely rivastigmine, donepezil and galantamine given in all stages of AD. Mematine is another class of drug known as NMDA receptor antagonist prescribe in moderate to severe AD. These drugs offer advantage for a limited period of time among 6-12 months. Other therapy is also available for the people who are suffering from AD. A nutraceutical compound known as huperzine A has show promising result in brain functions and in other daily exercise. Remarkably, no new type of drugs has been approved till now, and no near term approval are expected based on ongoing studies. ***(Weller2018)***

Future Treatment

Currently, there are no effective treatment is available to cure AD. Many studies are going in various phases of clinical trials but miserably no new drug has come out in the market. Therapies presently in phase 3 that concentrate on amyloid hypothesis. Which target the amyloid Precurssor Protien this protein can be broken with the help of secreterase enzyme. ***(Beta & gamma)(Ehab et al: 2019)***
Several drugs are under development in initial phase of clinical trials which target the spiral shaped amyloid beta with the help of beta blockers. Beta blockers will target the major portions of spiral shaped amyloid protein whose function is to maintaining their shape and stop the formation of NFTs and allowing the body to remove the A-B from the brain.There are many research are going in many phases of clinical trial in near future with lots of studies which are going on bring hope that we will able to get a distinctive pharmacotherapy for treatment for AD or slightly to delay the advancement of the disease. Lastly AducanumabIs a hope for many clinicians which show promising result in the treatment of AD for all stages of Alzheimer aducanumab is manufacture by the Biogen pvt ltd. ***(Desai 2003)***

VI. CONCLUSION

More than a century ago in year 1907, sir Alois Alzheimer was found the first patient suffering from the new neurological disorder, named Alzheimer disease in an old woman, from then to till now much research has been made to understand the pharmacological events occurring in AD, which is the leading cause of loss of memory (dementia) in old age. However, apart from the loss of memory (an individual problem), but on large scale it is one cause which enhancing social burden, increased morbidity and mortality in a country. They are several therapeutic treatments available worldwide, but all have mixed effectiveness, hence some scientists reported that exercise along with other medication will improve the AD in both pre and late stages by improving blood brain flow, increase hippocampal volume along with improving neurogenesis.

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Conflict of Interests

The authors declare that they have no conflict of interests.

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