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ALZHEIMER'S DISEASE: A PROGRESSIVE NEURODEGENERATION

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Abstract - *Alzheimer's Disease is age-associated Cognitive disorder. It is abbreviated as AD. The nature of the degeneration of neurons in AD is irreversible. The neuro-degeneration begins from the hippocampal region of the brain and then it spreads to the other parts of the brain thus resulting in the shrinkage of the brain. This neurodegenerative disease is characterized by two hallmark pathologies namely β-amyloid plaque deposition and neurofibrillary tangles of hyper-phosphorylated tau. It is characterised by severe loss of memory, changes in personality and unusual behaviour. AD can be early onset and late onset. The early onset are familial (less than 1 percent) whereas the late onset AD are age related (occurs in elderly). According to the World Health Organization (WHO) estimates, the overall projected prevalence in global population will quadruple in the next decades, reaching 114 million patients by 2050. Till date there is no cure for Alzheimer's Disease. The drugs known so far to slowdown the disease are available in the market namely Donepezil, Rivastigmine and Galantamine. The present review article focuses on information summarizing the History, Hypothesis, Diagnosis and Treatment of Alzheimer's disease.*

Key Words: Alzheimer's Disease, Acetyl Choline, Dementia, Beta amyloid, tau protein, Alzheimer's Hypothesis, Medicinal plants, Phytochemicals.

1. INTRODUCTION

Alzheimer's disease is abbreviated as AD. It is one of the leading cause of death among the other forms of dementia. It is referred as a 'progressive neurodegenerative disease' as the neurons get degenerated with time in the hippocampus, cortex and subcortical structures[1]. AD was discovered by German Psychiatrist and Neuropathologist Dr. Alois Alzheimer in 1907 when one of his patient Auguste, a 51 year old woman who suffered from a peculiar cerebral cortex disease. She had language problems, memory loss and unusual behaviour symptoms such as hallucinations, delusions, paranoia[2]. By seeking the permission from her family autopsy was carried out. Alzheimer examined her brain microscopically by using silver staining histological technique[3]. He observed accumulation of senile plaques in her brain. People above the age of 65 are more prone to AD. The etiology behind the Alzheimer's Disease is not known. However plaques and NFTs result in the accumulation of beta amyloid protein in between the neurons is seemed to be responsible. The decrease in the levels of Acetyl Choline may result in AD. Symptoms such as unusual behaviour, changes in personality, irritation, frustration, hostility[1], forgetfulness, language problems and difficulty in communication, learning and reasoning appear. The patient suffers alot emotionally, physically and require caretakers. The medicines to have a temporary control on this disease are available in the market. The person suffering from AD will require time to time medication, emotional support from friends and family. Though the proper reason for the disease is yet a mystery but hypothesis support that proteins such as beta amyloid and tau protein take part in causing the disease. Beta amyloid is present outside the neurons while tau protein is present inside the neurons. In order to fight the accumulation of these proteins the scientists, researchers and doctors have come up with treatments from time to time. The drugs so far showing some effectiveness are Rivastigmine, Galantamine, Donepezil, Tacrine, Memantine, combination of Memantine with Donepezil and are approved by the FDA. Apart from having a great social impact, this would clearly lead to increased economic burden to healthcare systems worldwide[11,12]. Still the research is being carried out to get the best and efficient drug to treat the disease. It is currently estimated that 46.8 million people worldwide have dementia with an estimated global cost of dementia care at US$818 billion in 2010[13].

2. HYPOTHESIS:

The human APP gene is located on chromosome number 21 and is about 240kb having around 18 exons[4,5]. The major beta amyloid peptide which encode proteins are 695, 751, 770 amino acids. APP751 and App770 are expressed in most of the tissues and contain a 56 amino acid Kunitz Protease Inhibitor. APP695 is expressed in neurons and lacks the KPI domain[6]. There are two ways through which AD is set to occur viz., Early onset and Late onset. The early onset AD is familial (5-10%) and the late onset is age associated.

The Beta amyloid protein, Tau protein and Acetyl choline are the credentials for causing Alzheimer's Disease. Hypothesis are mentioned below:

2.1 Beta-Amyloid Hypothesis:

Amyloid Precursor Protein is a trans-membrane protein and is normally cleaved by alpha-secretase and gamma secretase. The fragments of APP get degraded in the Proteasome, this is a normal process. On the other hand the APP is cleaved by Beta-secretase enzyme which leads

to the accumulation of beta amyloid outside the neurons. The communication between the neurons is cut down.

2.2 TAU Protein Hypothesis :

The TAU protein accumulates inside the neuron. Phosphorylated Tau are subunits of Paired Helical Filaments (PHFs), which form NFTs. The impaired microtubules affect axonal transport of proteins and eventually cause neuronal death[16]. As a result of phosphorylation[15] of Tau, the neuron cell shrinks and final end up being neurofibrillary tangle. This indeed affects the brain leading to sequence of symptoms such as memory loss, decision making, mood swings, irritation etc.

2.3 Acetyl Choline Hypothesis:

The gap between the neurons is called synapse. The Acetyl Choline is a neurotransmitter that helps in the communication between the neurons and is important in memory and learning. Under normal conditions the neuron releases the ACh into the synaptic cleft where it reacts with ACh receptor present on the post synaptic cleft. The enzymes AChE and BChE break down the Acetyl choline to acetate and choline thus terminating the signals. The acetyl choline esterase and Butyryl Choline esterase enzyme digests the Acetyl Choline which results in the loss of communication of between neurons. Thus causing cognitive impairment.

3. DIAGNOSIS :

3.1 Magnetic Resonance Imaging:

The MRI scan is normally operated by radiographer. In MRI strong Magnetic field and radio waves are used to produce a detailed image of the brain. The patient's body is scanned and imaging investigations are carried out. The internal organs suspected to be damaged are observed closely.

3.2 Computerized Tomography:

The detailed imaging of the blood vessels, bones and internal organs of the body. The CT scans are carried out by radiographers. The patient who is being subjected to scanning process is advised to avoid eating for many hours in order to get clear images of the particular organ. The patient should keep the health care staff if he is having allergy, kidney problems or diabetes. CT scan is not recommended if in case the patient is pregnant because the X-Rays may harm the baby. Thus the cross sectional images of the brain are produced by a specialised X-ray technology. It is presently used to examine tumours, strokes and head injuries.

3.3 Positron Emission Tomography (PET) :

Positron Emission Tomography is abbreviated as PET. PET is a technique which is used to to produce the 3-dimensional detailed image of brain and other internal organs of the body. This technique is useful in studying many conditions such as cancer, heart disease and brain disorders. Imaging the brain will give a clear idea about the AD.

3.4 Mental Status Examination:

Brief mental status check would be conducted by health care officials or more extensive set of tests to have access over thinking and memory. People having some kind of dementia say Alzheimer's are tested via Mini-Cog test and it takes only three minutes to administer[9].

3.5 Urinalysis:

Urinalysis is nothing but a Urine test. Routinely the urine analysis is carried out by the Doctors as one the tests for the diagnosis of Alzheimer's disease. Urine sample is taken to health care centres to determine the chances of getting Alzheimer's disease. The test detects isoprostanes, fatty acids that are formed as a result of free radical damage in the brain, the damage is correlated with clinical diagnosis of AD.

3.6 Mild Cognitive Impairment:

MCI causes little cognitive disability which can be measurable and noticeable. Moreover lies between early onset and late onset AD wherein the individual experiences memory loss, decline in thinking skills and intellectual dysfunction at a much higher rate. Some people may have fear of dementia and will have memory loss at much higher rate than one would expect.

3.7 Visual Clues to the Diagnosis of Dementia:

The visual clues are noticed in the patients. The noticeable characteristics such as change in personality, behavioural changes, anxiety, depression, hallucinations and appearance.

3.8 Lumbar Puncture test :

Lumbar puncture helps to diagnose the fatal infections of the central nervous system. This test is not commonly used. But it can give certain revelations about the rare diseases that could match the symptoms of dementia.

3.9 Mini Mental State Examination :

Mini Mental State Examination is abbreviated as MMSE. It is a 30 points questionnaire used to measure cognitive status of an individual. This is one of the most commonly used test used for the memory problems thus helping out in diagnosing the Alzheimer's Disease.

3.10 Electro Encephalo Gram (EEG) :

Electro Encephalo Gram is abbreviated as EEG. This test records the electrical patterns in the brain. The one's

suffering from the disease will have diffuse and symmetrical slowing of the brain waves that would register on EEG. It has become one of the important tool for the diagnosis of cognitive disorders.

4. TREATMENT:

Drug therapy for Alzheimer's disease is yet in it's infancy[2]. The treatment is huge challenge for the pharmaceutical companies in terms of cost, time and efficacy of drug. The Pharmacologic treatment is still not available as of now. The US drug and administration has approved six drugs for AD treatment such as Rivastigmine, Galantamine, Donepezil, Tacrine, Memantine and combination of Memantine with Donepezil. These drugs improve the symptoms by increasing the neurotransmitter chemicals in brain[7]. For mild to moderate AD, Rivastigmine and Galantamine have been approved. Donepezil is approved for all the stages of AD[2]. Some medicinal plants, phytochemicals studies have been reported to have compounds namely flavonoids, liganans, sterols, polyphenols and alkaloids show a wide variety of anti-cholinesterase, anti-oxidant, anti-amyloidogenic activities[1]. The polyphenolic phytochemicals like Curcumin, Resveratrol and EGCG can pass through Blood Brain Barrier and have potential anti-oxidative as well as anti-inflammatory properties[8]. Phytochemicals are also protective against other Cognitive disorders like Parkinson's Disease and Huntington's Disease[8]. The future of treatment of Alzheimer's disease lies in the targeting of neuritic plaques (NPs) and neurofibrillary tangles (NFTs), which have the potential to delay neurodegeneration[14].

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