An overview on the aetiology and treatment of Alzheimer's disease.

Abstract- Alzheimer's disease is a disease that mainly leads to the degeneration of cells in the brain and it causes dementia. This reduces thinking capacity and doesn't allow the person to be independently do their own work. Two main causes of AD are cholinergic and amyloid hypothesis. Other risk factors include age, genetics, infections in the brain etc. currently only two types of drugs can treat AD, cholinesterase enzyme inhibitors and NMDA antagonists, but these are only able to treat the symptoms not the whole disease. At this moment the researchers are trying to target several mechanisms such as abnormal tau protein metabolism, inflammation and damage in the cholinergic system.

Keywords- Alzheimer's disease; neurodegeneration; amyloid peptide; tau protein; risk factors; disease-modifying therapy; chaperons; heat shock proteins

1. Introduction

This disease is mainly the cause of dementia, and it can be defined as a slow progressive neurodegenerative disorder that is characterized by neurotic plaques because of amyloid beta-peptide accumulation in the affected part of the brain.

The German psychiatrist Alois Alzheimer, while treating his first patient who was suffering from loss of memory and personality change, noted that there were amyloid plaques and a huge loss of neurons in his brain. Sadly, this patient died before he could treat him.

There are currently 50 million patients and it's expected to reach 152 million by the next 28 years

2. Diagnostic criteria for Alzheimer's disease.

Patients must undergo tests like neurological and pathological examination and should also undergo test like the MRI. According to some studies, vitamin (vit.) B12 deficiency is and neurologic problems are at a massive risk to the disease. Deficiency of vitamin (vit.). Homocysteine levels can be used for detection of the deficiency of vitamin B12. This is

because it causes brain damage and apoptosis. Hence if the serum is measured for Homocysteine levels in them then Vitamin B12 levels can be checked.

NINCDS and ADRDA developed a working committee to set up a disease specific requirement for AD

This criterion includes:

1. AD is probable if dementia is confirmed by neuropsychological tests like memory loss, aphasia, apraxia, agnosia. These symptoms start from age 40 and can extend to age 90.

2. AD can also be possible if there are not neurological or psychiatric disorders, but there is presence of certain other illness or brain disorders and they may not be the main reason for dementia.

3. AD is confirmed when there is a biopsy or autopsy which confirms the disease histopathologic ally.

Biomarkers for Alzheimer's disease fall into two categories:

(a) markers for amyloid in the brain, like PET and CSF placement.

(b) neuronal injury markers for CSF such as tau and atrophy measurement by MRI

3. **AD Neuropathology**

   Most of the neuropathological changes that occur are related to progression and symptoms of the disease; like (a) lesions caused by accumulation of amyloid plaques and neurofibrillary tangles and other types of deposits that are found in the patient's brain. (b) negative lesions or lesions due to loss, are mainly due to huge atrophy of neural and synaptic loss.

   I. Senile plaques-

      These plaques are initially extracellular deposits of beta amyloid protein, and can come in a variety of shapes and sizes, such as thick cored or compact plaques. These transmembrane amyloid precursor protein (APP) gets deposited due to proteolytic cleavage enzymes like secretase. Large, insoluble amyloid fibrils can clump together to create plaques, and oligomers can spread throughout the brain to generate amyloid-beta monomers.

      Neurofibrillary Tangles (NFTs)

These are abnormal filaments that are twisted to form helical paired filament and accumulate in whole of the neuron. This leads to loss of cytoskeletal microtubules and other associated protein.

This tau protein is the major part of NFT. The morphological stages of NFT are:

a. Pre tangle phase, here the NFT are accumulated in the somatodendritic compartment

b. Mature phase, the nucleus is displaced to the periphery

c. Extracellular tangles, loss of neurons due to huge amounts of protein and also with partial resistance to proteolysis.

II. Loss in synapse

The synaptic damage involves in defect of axonal transport, mitochondrial damage and other factors. This is also increased due to accumulation of the amyloid-beta and tau protein in the synapses. This leads to dystrophy of pre-synaptic terminals, dendritic spines and axon.

4. The Stages of AD

These phases of the disease are classified into

(1) pre-clinical- this may last for several years and is characterized by mild amnesia. Early pathogenic alterations in the cortex and hippocampus are also caused by it.

(2) The mild stage- here the patient start experiencing problems like loss in concentration and memory loss. There is also a change in mood and the onset of depression.

(3) Moderate AD- here the disease reaches the pallium area and leads to trouble recoginizing family and friends. Here there is a loss of impulse control, reading and writing difficulty.

(4) Severe AD- here the disease reaches the cortex and there is severe accumulation of neurotic plaques and neurofibrillary tangles. Patients here are bedridden and cannot even swallow food. Difficulty in urination is also prevailing in this case.

5. AD- Causes and Risk Factors

Age, genetic variables, head injuries, infections, and other factors are found to be the risk factors of the disease. The main reason for the occurrence of the disease is still unknown. Many ideas have been offered as causes for AD, but two are thought to be the most important: some feel that cholinergic dysfunction is a major cause of AD, while others believe that primary factors is the changes in the APP.

I. **Disease Hypotheses of AD**

a. Cholinergic Hypothesis

The enzyme choline acetyl transferase more popularly known as ChAT leads to the production of acetylcholine, was linked to neocortical and presynaptic cholinergic deficiencies in the 1970s (ACh). amyloid cholinergic theory of AD was theorized because of the importance of ACh in memory. The ChAT enzyme synthesizes ACh from choline and acetyl coenzyme amyloid, and the vesicular acetylcholine transporter (VAChT) transports it to synaptic vesicles. ACh has a role in a variety of physiological processes in the brain. Cholinergic neuron degeneration has been discovered to occur in Alzheimer's disease, causing changes in maintaining the memory function. B-amyloid is thought to interfere with cholinergic neurotransmission, causing a decrease in choline absorption and the release of ACh. This along with loss in cholinergic synaptic loss have been linked to the neurotoxicity of amyloid oligomers and interactions between AChE and amyloid peptide in studies. Compounds that promote acetylcholine synthesis can be used to counteract this effect. As a result, this hypothesis can be formed on three concepts; the presence of less presynaptic cholinergic markers in the cerebral mantle, NMB degeneration in the basal forebrain, and importance of cholinergic antagonists in the memory loss.

b. Hypothesis of Amyloid protein

An alternating hypothesis for the Non-Inherited AD (NIAD) but for now Amyloid hypothesis is mainly accepted for Inherited AD. It was recognized that abnormal deposition of beta sheets of amyloid protein in the CNS causes dementia. The amyloid hypothesis says Amyloid-Beta degradation is decreased by age or pathological criteria, and this leads to the increase in Amyloid-Beta peptides and leads to neurotoxicity and tau pathological induction. This leads to necrobiosis and neurodegeneration.

II. Risk Factors for AD

A. Ageing

Aging is the most major risk factor in Alzheimer's disease. Younger people are infrequently affected, and most cases of Alzheimer's disease develop

beyond the age of 65. This is an irreversible and a very complex which leads to decrease in brain volume and weight. It also leads to loss of synapses and expansion of ventricles in certain places of the brain. Furthermore, various disorders such as hypermetabolism of glucose, dyshomeostasis of cholesterol, mitochondria malfunction.

B. Genetics

Over time, genetic variables have been shown to play a significant influence in the development of Alzheimer's disease. The majority of cases of EOAD are autosomal dominantly inherited, and mutations in dominant genes such as (APP), (PSEN-1), (PSEN-2), and (ApoE) have been related to AD.

Amyloid Precursor Protein (APP)

The APP gene on chromosome 21 encodes a type I transmembrane protein that is cleaved by α-, β- and -secretase to release amyloid and other proteins. In the APP gene, thirty mutations have been discovered, twenty-five of which are linked to AD and induce a buildup of amyloid in high concentrations.

Presence of NFTs and Amyloid-Beta, activation of microglia as well as astrocytes is seen in the neuropathological reports.

Presenilin-1 (PSEN-1) and Presenilin-2 (PSEN-2)

PSEN1 and PSEN2 genes are mainly homologous and have 67% similarity and a difference in the N terminus region. Mutation in the former is more common, over 200 now. But there is only 40 odd mutations for PSEN2. PSEN1 can be a protein that activates the gamma secretase complex. Other studies of PSEN1 shows dysfunction and impairment of memory in mice.

Apolipoprotein E (ApoE)

ApoE protein is a glycoprotein that is abundantly produced in liver and brain astrocytes, as well as certain microglia, and acts as a receptor-mediated endocytosis ligand for lipoprotein particles like cholesterol, which is necessary for myelin production and appropriate brain function. Because of SNPs that modify the coding sequence, this genome contains three isoforms: ApoE2, ApoE3, and ApoE4. The ApoE4 allele is associated with a greater risk factor.

ATP Binding Cassette Transporter A1 (ABCA1).

It is one of a broad family of ABC transporters that maintain cholesterol efflux into the brain, similar to apolipoproteins-AI (ApoAI) and ApoE. ABCA1 also maintains lipidation of ApoE stability and acts as a mediator for High density lipoprotein production. ABCA1 deficiency promotes formation of the plaques and prevents lipidation of ApoE, according to studies in AD mice. Tangier illness is characterised reduced concentrations of HDL and ApoAI in plasma, cholesterol buildup in tissues, and AD development in humans due to a mutation in ABCA1.

Bridging Integrator 1 (BIN1) and Clusterin Gene (CLU)

These two are new risk factors and CLU is discovered on chromosome 8 and increased in the cortex and hippocampus of the brain of the patient. CLU has neuroprotective effect by combining with Amyloid and increasing its elimination. Amyloid values shows the neuroprotective or neurotoxic effect of the CLU.

Evolutionarily Conserved Signaling Intermediate in Toll pathway (ECSIT)

High amounts of accumulation of Amyloid Beta in the AD brain leads to the increase in the protein oxidation and this shows the high importance of the mitochondria in the cytotoxicity of Amyloid-beta. This genes was found on chromosome 19. It stabilizes mitochondrial respiratory complex and acts as a cytoplasmic protein which helps in the same. Activation of nuclear factor and activation protein is done by the Adaptor protein.

Estrogen Receptor Gene (ESR)

Both men and women are affected by Alzheimer's disease, but women account for roughly two-thirds of all cases. Women with Alzheimer's disease suffer worse mental degeneration than men, according to several studies. Furthermore, some genetic variations, such as the ApoE4 allele. This increases the AD risk in women than in men, considerably.Some of the other litearature has found out that ovarian hormones during menopause is linked to an increased risk of Alzheimer's disease in women. Estrogen is responsible in regulation of several activities of the brain like stress, reduction of Amyloid peptide levels and many more. Hence ESR is the gene which controls the activity of estrogen.

Other Genes

Polymorphism in the vitamin D receptor (VDR) gene, which alters vitamin D binding to its receptor and may induce neurodegenerative diseases and neuronal injury [73], is another gene polymorphism linked to an increased risk of AD. Furthermore, epigenetic variables such as DNA methylation, histone changes, and chromatin alterations have been shown to play a role in Alzheimer's disease.

C. Environmental Factors

Air Pollution

All cases of Alzheimer's disease cannot be explained by ageing or genetic risk factors. Air pollution, nutrition, metals, infections, and a variety of other environmental risk factors may cause inflammation, raising the likelihood of developing Alzheimer's disease. The most important environmental elements and their correlations with AD are discussed in this article.

NAAQSs has defined 6 air pollutants in the USA and these include ozone, carbon monoxide, nitrogen dioxide, sulfur dioxide, particulate matter, and lead. This pollution leads to the formation of Amyloid- Beta 42 formation and accumulation and leads to impaired cognitive function.

Diet

Antioxidants, polyphenols and fish are some of the dietary supplements that have been shown to reduce the risk of Alzheimer's disease, but saturated fatty acids and a high-calorie diet have is responsible for the increased problems of the disease Non-enzymatic glycation of free amino groups in proteins, lipids, and nucleic acids results in the destruction of heat-sensitive micronutrients, the loss of substantial quantity of water, and the production of hazardous secondary products.) The capacity of AGEs to produce oxidative stress and inflammation is referred to as their hazardous effect. This is achieved by altering structure of the receptors and body proteins. AGEs levels in the blood have been linked to cognitive loss and the advancement of Alzheimer's disease in several investigations.

Metals

Aluminum is widely employed in a variety of industries, including processed foods, cosmetics, medical preparations, and medications. Aluminum is attached to plasma transferrin and citrate molecules in the body, which can promote aluminum transfer to the brain. Aluminum in the brain interacts with proteins and causes misfolding agrégation and phosphorylation proteins like tau.

Infections

Chronic infections of the central nervous system (CNS) can lead to the formation of amyloid plaques and NFT, making them one of the risk factors for Alzheimer's disease. Dr. Itzhaki's research identified herpes simplex virus (HSV-1) DNA among ApoE-4 allele carriers, explaining the elevated risk of acquiring Alzheimer's disease. HSV-1 can proliferate in the brain, triggering an inflammatory response and increasing amyloid deposition, causing in neuronal damage and the progression of Alzheimer's disease. Miklossy and Balin's research, on the other hand, established the involvement of chronic bacterial infections in Alzheimer's disease.

D. Medical Factors

Alzheimer's disease is associated with a number of risk factors. To add to this, older adults with Alzheimer's disease are more likely to have medical disorders like cardiovascular disease (CVD), obesity, diabetes, and others. All of these disorders are linked to an increased risk of Alzheimer's disease.

Cardiovascular Disease

Cardiopathy affects leads to insufficient supply of blood to the body and the brain. This leads to neural damage and hypoxia. The CHD hypothesis says that atherosclerosis, hypoperfusion and emboli leads to the increased risk of AD. Hypertension leads to the decrease in the arterial lumen size of the leads to cerebral edema and hence participate in the risk factor of AD.

Obesity and Diabetes

Increased amount of body fat may lead to the less brain blood supply which in turn leads to ischemia and cognitive state, and vascular dementia. This can also lead to IGT or diabetes. Chronic IGT may lead to high amount of accumulation

of amyloid beta. Obesity is a function to stimulation of macrophages and lymphocytes. This causes systemic inflammation and hence may lead to hyperglycemia. This may lead to heart diseases and hence leading to the increase in the risk factors of AD.

6. THE 2010s: THE ERA OF BIOMARKERS

In the last 20 years, significant progress has been achieved in finding in vivo biochemical markers of Alzheimer's disease. Several researchers improved their ability to identify and analyse amyloid (the plaque's major ingredient) and tau levels in the cerebrospinal fluid. protein (a component of the neurofibrillary tangle) that had been found

Indicative of Alzheimer's disease (AD) pathology in the brain. Klunk and his associates

Pittsburgh was founded by (see Mathis et al., 2003).

compound-B ([11C]-PIB), a binding agent for amyloid, is being developed. PET imaging can identify amyloid buildup in the brain.

Agents that bind to tau in the brain and can be used with PET imaging have also lately been developed. Despite its widespread acceptance, there is mounting evidence that the amyloid cascade hypothesis is flawed, particularly in terms of the invariant temporal sequence of pathogenic events (Drachman, 2014).

7. Treatment

Alzheimer's disease affects roughly 24 million people globally, and the overall number of persons with dementia is expected to climb fourfold by 2050. Despite the fact that Alzheimer's disease is a public health concern, there are currently just two kinds of medications approved to treat it: cholinesterase inhibitors (naturally occurring, synthetic, and hybrid variants) and N-methyl d-aspartate antagonists (NMDA). Multiple physiological processes in Alzheimer's disease damage Ach-producing cells, reducing cholinergic transmission in the brain.

Unfortunately, only a few clinical trials on Alzheimer's disease have been launched in the recent decade, and all of them have failed miserably. To further understand AD pathophysiology and create effective treatments, several pathways have been hypothesised, including aberrant Tau protein metabolism, -amyloid, inflammatory response, and cholinergic and free radical damage are all factors to consider. Most modifiable risk factors for Alzheimer's disease, such as cardiovascular or lifestyle variables, are adjustable. behaviors, can, on the other hand, be avoided without medical intervention. It increases

brain health and lessen Alzheimer's disease through activating brain vascularization, plasticity, and neurogenesis due to physical activity. Furthermore, the MD, intellectual exercise, and higher education may all help to slow the onset of Alzheimer's disease and memory loss while also increasing brain capacity and cognitive abilities.

A. Cholinesterase Inhibitors

The cholinergic hypothesis states that AD is caused by a decrease in acetylcholine (ACh) production. One of the therapy options for improving cognitive and neural cell performance is to enhance cholinergic levels by inhibiting acetylcholinesterase (AChE). AChEIs stop acetylcholine from being degraded in synapses, resulting in a buildup of ACh and stimulation of cholinergic receptors.

For Alzheimer's disease tacrine was the first FDA approved drug and it was taken of the market due to its side effects like hepatotoxicity. Later rivastigmine and donepezil were developed and are now used for the treatment of AD.

By increasing the choline reuptake, acetyl choline synthesis in is increased in the presynaptic terminals. This can be done by targeting CHT1 which is responsible in the supply of the choline for ACh synthesis.

Donepezil

Donepezil is an indanonebenzylpiperidine derivative that belongs to the second generation of AChEIs and is widely used to treat Alzheimer's disease. Donepezil inhibits acetylcholine hydrolysis by binding to acetylcholinesterase in a reversible manner, resulting in a greater levels of ACh at synapses. The medication is well tolerated, with very minor and temporary cholinergic adverse effects affecting the gastrointestinal and neurological systems

Rivastigmine

BuChE activity is largely located in glial cells in the normal brain, with only 10% of AChE activity, however it is elevated to 40–90% in the AD brain, while ACh activity is lowered simultaneously, suggesting that BuChE activity may signal a mild to severe dementia. The medication is used to treat mild to moderate Alzheimer's disease. It enhances cognitive abilities and daily tasks. Rivastigmine is available as transdermal patches, which provide regulated and continuous medication delivery through the skin, resulting in improved tolerability and

caregiver satisfaction. In addition, as compared to pills, patches can give a lower dosage, resulting in fewer adverse effects. Most Alzheimer's patients have memory loss and swallowing issues, which make it difficult for them to take their medications on a regular basis. As a result, transdermal patches are the most effective way to give the medicine to Alzheimer's patients.

Galantamine

For mild to severe Alzheimer's disease, is regarded a conventional first-line treatment. To transport GAL hydrobromide, Misra et al. and Fornaguera et al. employed solid-lipid nanoparticles and nano-emulsification, respectively. The findings of these investigations revealed a promising technique for drug delivery that is both safe and effective.

B. N-methyl d-aspartate (NMDA) Antagonists

The stimulation of this leads to the influx of calcium ions which sends a signal transduction and triggers a gene transcription which is essential for the formation of LTP and is required for memory formation and plasticity. Over stimulation of the same leads to the high amount of influx of calcium ions, and hence leads to excitotoxicity.

C. Memantine

Memantine is a low-affinity noncompetitive antagonist of the NMDAR, a glutamate receptor subtype that prevents overactivation of the glutaminergic system, which causes neurotoxicity in Alzheimer's disease. Either alone or in combination with AChEI this is used in the treatment of mild AD. Because it inhibits excitatory receptors without interfering with normal synaptic trans mission, the medication is both safe and well tolerated. The latter is linked to a slew of negative side effects, particularly in terms of learning and memory.

5 Conclusions

As a consequence, the National Institute on Aging-Association Alzheimer's reclassified and changed the 1984 NINCDSADRDA criteria to improve specificity,

sensitivity, and early identification of persons at risk of Alzheimer's disease. Clinical biomarkers, body fluids, and imaging tests have all been recommended as criteria for a more accurate diagnosis of Alzheimer's disease. Despite this, the treatment of Alzheimer's disease remains symptomatic, with little change in the prognosis of the disease. Galantamine, donepezil, and rivastigmine are cholinesterase inhibitors, while Memantine and other NMDA antagonists improve memory and attentiveness without preventing development.. Many studies have shown that changing your lifestyle habits, such as nutrition as well as exercise, can help to boost brain health and minimize symptoms of Alzheimer's disease (AD) without requiring medical intervention and is recommended as first-line treatment for all patients with AD.

Recently, research has focused on pathological aspects of Alzheimer's disease, such as amyloid and ptau.Future treatments leading the path of amyloid, such as An1792, Solanezumab, Bapineuzumab, Semagacitystat, Avagacestat and Talenfurbil, have seized clinical trials but have not demonstrated to demonstrate efficiency in the last steps.

In conclusion, the success of the appointment of the announcement depends on its first administration and monitoring of the patient for the progression of the disease that uses the diagnosis of biomarkers.

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