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AN EXTENSIVE STUDY ON ALZHEIMER'S DISEASE

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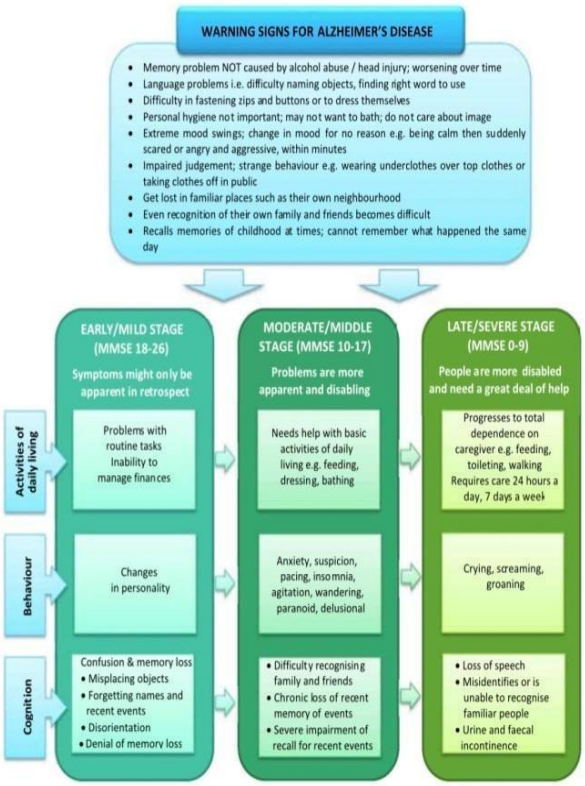
ABSTRACT
Alzheimer's disease is one of the most devastating brain disorders of elderly humans. It is an undertreated disease becoming a major public health problem with a witness of increasing cases from the last decade. This article reviews about the increasing efforts directed for the discovery of modern etiological, clinical trials on varied cognitive and behavioural functions of brain and novel diagnostic and therapeutic development thesis for AD . The COVID-19 pandemic had a particularly detrimental effect on older population and patients with dementia, with an enormous death across the world. Hence, this review article also focusses about the morbidity and mortality rate of patients with AD.

KEYWORDS: Alzheimer's disease, β-amyloid plaques, APOE.E4 Gene, Biomarkers, cognitive impairment, Gene therapy, COVID-19.

INTRODUCTION

Alzheimer's disease is a progressive, neurodegenerative disease that impairs memory and cognitive judgement and is often accompanied by mood swings, disorientation and eventually delirium. It is the most common cause of dementia (complete loss of memory and activities). AD is currently ranked as fifth leading cause of death among 65 years old population's and ranked third among all other aged individuals. This corresponds to 350,000 new cases of early onset dementia per year globally. By 2025, an estimated 7.2 million Americans are expected to have AD accounting for 60-80% of cases, in the absence of medical breakthrough, the Prevelance is expected to climb to 13.8 million by 2060, almost doubling the number currently affected.

AD typically manifests through the presence of extracellular plaques of insoluble β- amyloid peptides (aβ) and neurofibrillary tangles (NFT) containing hyper phosphorylated tau protein (p-tau) in the neuronal cytoplasm. Of patient's brain, thus aiding to loss of connection between nerve cells and neurons in brain.



MULTIFACTORIAL COMPONENTS CONTRIBUTING TOAD

Although, It's unknown what triggers alzheimer's disease, several factors are known to increase your risk of developing the condition.

They include

1. AGING: combination of age-related changes in brain such as reduction in brain volume and weight, a loss of synapses and ventricle's enlargement in specific areas accompanied by SP deposition and NFT.

2. GENETICS: Mutations found in APP gene (located in chromosome 21q21) and differences in the frequency of allele pairs of APOE.E4 gene are shown to have greatest impact. Apart from this mutations in PSEN1 gene (located at 14q24.3) are associated with 80% of cases of early-onset AD, whereas 5% 0f cases are associated with mutations in PSEN2 gene [located at 1q31.q42]. Down syndrome [Trisomy in chromosome 21]

3. ENVIRONMENTAL AND LIFESTYLE MODIFICATIONS: Environmental factors including air pollution, pesticides, metals [using aluminium pans] might increase the risk of developing symptoms.

Lifestyle factors include stress, diet [saturated fatty acids and high calory intake], vitamin deficiency, smoking contribute to increase the risk of alzheimer's disease.

4. CLINICAL FACTORS: Vascular diseases like Hypertension; obesity, type2 diabetes mellitus, secondary infections like pneumonia and other bacterial infections. cerebro-vascular injuries including hemorrhagic infarcts, large ischemic cortical infarcts and vasculopathies, TBI, cancer are various clinical factors aiding to alzheimer's disease.

- Exaggerated abundance in blood of potentially toxic fat-protein complexes can damage microscopic brain blood vessels called capillaries and thereafter, leak into brain, causing inflammation and brain cell death. So changes in dietary behaviours and certain medications could potentially reduce blood concentration of these toxic fat protein complexes reduces the Alzheimer's disease.
- AD can be caused by reactivation of virus, such as during a cold sore flare up, which increases a person's risk of developing AD.

5. ESTROGEN: a number of studies have shown that the APOE-e4 genotype have a stronger association with alzheimer's dementia and neurodegeneration in women than in men. Some evidences have suggested that it is because of an interaction between the APOE genotype and the sex hormone estrogen. Some of the researches have shown that oestrogen therapy taken around the time of menopause was associated with a lowered risk of dementia in older age, but when taken in late life was linked with an increased dementia risk.

6. RADIATION: Some recent studies have shown that ionising radiation from medical equipments is also another confounding factor for AD, as they induce vascular abnormalities, demyelination and shifts the proliferative response of progenitors from neurogenesis to gliogenesis.

DIFFERENT HYPOTHESIS ABOUT AD

1) AMYLOID HYPOTHESIS

AD is caused by abnormal build up of proteins in and around brain cells. one of these proteins is called amyloid, deposits of which forms amyloid plaques by the action of enzyme β-secretase; this was taught to be the major causative of AD. This Hypothesis suggests that deprivation of Aβ plaques by acting of γ-secretase enzyme and β-secretase enzyme can help in acquiring required therapeutic outcome of AD. INTERVENTION: For targeting γ-secretase and β-secretase, undesirable side effects are inevitable like Notch signalling problems and blindness respectively.

CONCLUSION: Although the bulk of data supports role of Aβ as primary initiator of pathogenic cascade in AD, more researches have found that Aβ acts as a trigger in early disease process and appears to be necessary but not sufficient late stage of AD.

2) TAU HYPOTHESIS

NFT'S are other hallmark of AD, which are being targeted after the numerous failures of Aβ-targeting drugs as many studies suggest that tau pathology is more linked to progression of Alzheimer's disease.

CONCLUSION: As increased hyperphosphorylation of Tau proteins will render to more protein aggregation trials are being done to develop Tau aggregation blockers.

But these remained challenging due to lack of sensitive biomarkers for diagnosis and response –monitoring and the other tau-targeting strategies like stabilizing microtubules and manipulating kinases have just been tested.

3) INFLAMMATION HYPOTHESIS

Reactive gliosis and neuro inflammation are the hallmarks of AD. There is an increasing evidence stating that microglia emerges as the central cause of AD due to its various functions like synaptic pruning etc. Recent advances in understanding microglia dysfunction in pruning regulating plasticity etc. enhanced development of new opportunities in treating AD. However, there is a need for new biomarkers to this research.

4) CHOLINERGIC AND OXIDATIVE STRESS HYPOTHESIS

Acetyl choline is an important neurotransmitter which is involved in several physiological process such as memory, learning, attention sensory information etc. degeneration of cholinergic neurons takes place in AD leading to acetyl choline deficiency which disrupts extratelencephalic projection neurons in pre frontal cortex of brain.

Thus, treatment for this degeneration by cholinesterase

inhibitors was a glimmer of hope in AD patients.

AD is associated with cellular oxidative stress including augmentation of protein, oxidation, glycoloxidation, protein nitration as well as accumulation of Aβ.

Thus treatment with anti-oxidant compounds would provide protection against oxidative stress and Aβ Toxicity.

But it was challenged for its potency to stop the progression of AD and still many researches are being done to prove its potency.

5) Lastly, the NATIONAL INSTITUTE ON AGING – ALZHEIMERS ASSOCIATION (NIA-AA) framework hypothesizes that there is an silent stage of AD, in which the individual appears not to have the cognitive impaired symptoms.

Researches have been going on to measure the prevelance of this preclinical AD with sensitive biomarkers.

EFFECT OF COVID-19 PANDEMIC ON ALZHEIMERS DISEASE

Alzheimer's disease has emerged as a key comorbidity of corona virus disease caused by (SAARS-COV-2). The mortality and morbidity rate are elevated in AD due to multiple pathological changes like

i. Excessive expression of viral receptor angiotensin converting enzyme.
ii. COVID-19 is also been reported to cause cognitive impairment due to long term hospitalization and isolation, post COVID -19syndrome.

Thus, it posed a new challenge in preventing AD.

DIAGNOSTIC CRITERIA

- An early research suggests a new blood test that identifies a variant of protein p53 appears to predict AD progression up to 6 years in advance of a clinical diagnosis – precivity AD
- Vitamin B12 deficiency leads to oxidative stress that further aids to AD. so a special marker of vitamin B12 deficiency is elevated homocysteine levels. Diagnosis of vitaminB12 deficiency can be done by measuring vitamin B12 Levels alongside serum homocysteine levels test.
- MRI for neurons
- Chronic chromatic encephalopathy (CTE) is a neuropathologic diagnosis (characterised by brain changes that can only be identified at atopsy). Associated with repeated blows to the head
- Glucose hypo metabolism also a contributing factor for AD and this can be showed on PET scan.
- Biomarkers tests like PET brain imaging and analysis of proteins in blood and cerebrospinal fluid to identify the phase of disease with which the patient is suffering.
- While research settings have the tools and expertise to identify some of the early changes of AD, additional research is needed to fine-tune the tools accuracy.

NOVEL THERAPEUTIC APPROACH

None of the drugs available today for alzheimer's disease slow or stop the damage and destruction of neurons that cause AD symptoms.

- The U.S FDA has approve five drugs – RIVASTIGMINE, GALANTAMINE, MEMANTINE, DONEPEZIL, MEMANTINE combined with DONEPEZIL.
- A sixth drug, ADUCANUMAB is under review for potential approval. As it is the only one that may potentially slow the progression of Alzheimer's, as it has been tested on individuals with MCT and early Alzheimer's dementia.
- Three cholinesterase inhibitors [CI's] are currently available and have been approved for the treatment of mild to moderate AD. It includes DONEPEZIL, RIVASTIGMINE, GALANTAMINE.
- The drug SARGRAMOSTIM [Leukine] is currently in research, as it is thought that the drug stimulates immune system to protect brain from harmful proteins.
- To treat Behavioural and psychological symptoms of dementia [BPSD] CI's, memantine are used. Recent studies have shown that SEROTONIN REUPTAKE INHIBITORS are largely considered to be among the most efficient anti-depressants to treat comorbid depression in AD dementia.
- IMMUNOTHERAPY It utilizes antibodies that are either developed in lab/induced by the administration of a vaccine to attack the amyloid and promote its clearance.
- Another molecule undergoing testing is colostrinin a protein-rich polypeptide complex derived from sheep colostrum that inhibits Aβ aggregation and neurotoxicity in cellular assays and improves cognitive performance in animal models.
- GENE THERAPY, For APOE4 Homozygote of AD is actively reuniting patient's that have two copies of APOE4 gene. The study will assess the efficacy, safety and toxicity of viral injection into CSF.

CONCLUSION

Alzheimer's disease is a neurodegenerative, multifactorial, progressive disease that occurs due to accumulation βamyloid plaques and NFT'S which is leading to cognitive and behavioural impairment aiding to various symptoms like loss of memory, thinking ability, eventually loss of doing simple activities. There are various risk factors contributing to alzheimer's which include age, genetics, clinical factors, estrogen, etc. various hypothesis have been developed to know the underlying cause and proper therapeutic management of the disease. Clinical trials are being done for the development of accurate therapy for the disease, but these remained challenging due to lack of some sensitive biomarkers for diagnosis. And the developed medication

has not been completely proved to cure the disease they are just used to improve the condition of the patients. There is a huge need for the development of novel and sophisticated technologies for the appropriate cure as this disease is remaining as a major health concern.