Review on Alzheimer's Disease

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Abstract - In recent years great number of studies have achieved giving undertaking results in Alzheimer 's Disease (AD) discovery using automatic language processing.[1]The aim of this study is to investigate the main risk factors that affect and increase Alzheimer's disease progression over time even in cases with no significant memory impairment present.[3] Alzheimer's disease, the commonest cause of dementia, is a growing global health concern with huge implications for individuals and society. [2] The dramatic increase in the population with dementia expected in the next decades is accompanied by the establishment of novel and innovated methods that will offer accurate and efficient detection of the disease in its early stages.[3] Currently, there is a pressing need to shift the focus to accurate detection of the earliest phase of increasingly preclinical Alzheimer's disease (AD). [4] Its prevalence will increase considerably in the years to come, in pace with the increasing proportion of older people.[5] Accurate diagnosis at an early stage is the need of the hour for initiation of therapy.[6] Alzheimer's disease (AD) is a neurodegenerative disorder that nowadays affects more than 40 million people worldwide and it is predicted to exponentially increase in the coming decades.[7] Modern clinical diagnostic criteria have been developed, and criteria have also been proposed to recognize preclinical (or presymptomatic) stages of the disease with the use of biomarkers.[8] Despite the fact that Alzheimer's disease (AD) is the most common cause of dementia, after many years of research regarding this disease, there is no casual treatment. [9] Alzheimer's disease (AD) is one of the most common illnesses affecting large populations across the world, Also this disease is a form of dementia accounting for 60% to 80% of all cases of dementia.[10]

Keywords Alzheimer's disease, treatment, pharmacological therapy, neuroinflammation

INTRODUCTION

The worldwide prevalence of dementia is estimated to be over 45 million people.[14]Alzheimer's disease (AD) (named after the German psychiatric Alois Alzheimer) is the most common type of dementia and can be defined as a slowly progressive neurodegenerative disease characterized by neuritic plaques and neurofibrillary tangles as a result of amyloid-beta peptide's (Aβ) accumulation in the most affected area of the brain, the medial temporal lobe and neocortical structures.[11]

Neuritic plaques and neurofibrillary tangles represent the pathological hallmarks of AD, and are respectively related to the accumulation of the amyloid-beta peptide (Aβ) in brain tissues, and to cytoskeletal changes that arise from the hyper phosphorylation of microtubule-associated Tau protein in neurons. [12]

Genetic, biochemical, and behavioral research suggest that physiologic generation of the neurotoxic Aβ peptide from sequential amyloid precursor protein (APP) proteolysis is the crucial step in the development of AD.[13] One of the possible therapeutic strategies entails the elimination of such deposits by inhibiting Aβ aggregation.[15]

AD is considered a multifactorial disease: two main hypotheses were proposed as a cause for AD, cholinergic and amyloid hypotheses. Additionally, several risk factors such as increasing age, genetic factors, head injuries, vascular diseases, infections, and environmental factors play a role in the disease. [11]

The cause of the sporadic form of the disease is unknown, probably because the disease is heterogeneous, caused by ageing in concert with a complex interaction of both genetic and environmental risk factors .[16] Alzheimer's disease/dementia is contributing to the global non-communicable disease burden, and it is a leading source of morbidity and mortality in the aging population.[17]

The share of individuals aged 60 years or older is projected to increase to nearly 20% of the total Indian population by 2050 (319 million), accounting for 15.4% of individuals aged 60 and older worldwide and Also India faces an alarming potential increase in the number of people with dementia, India is home to 1.37 billion people, comprising 18% of the total world

population in 2019, and is set to surpass China as the world's most populous country in 2023.[18]

SIGNS AND SYMPTOMS

Alzheimer's disease is a progressive condition, which means the symptoms develop gradually and become more severe over the course of several years. It affects multiple brain functions.

The mild or early stage of AD, where several symptoms start to appear in patients, such as a trouble in the daily life of the patient with a loss of concentration , memory, disorientation of place and time, a change in the mood, and a development of depression and various symptoms are as follows:-

- Memory loss that disrupts daily life
- Poor judgment, leading to bad decisions
- Loss of spontaneity and sense of initiative
- Losing track of dates or knowing current location
- Taking longer to complete normal daily tasks
- Repeating questions or forgetting recently learned information.
- Trouble handling money and paying bills
- Challenges in planning or solving problems
- Wandering and getting lost
- Losing things or misplacing them in odd places
- Difficulty completing tasks such as bathing
- Mood and personality changes
- Increased anxiety and/or aggression.

Moderate AD stage, in which the disease spreads to cerebral cortex areas that results in an increased memory loss with trouble recognizing family and friends, a loss of impulse control, and difficulty in reading, writing, and speaking .[11]

The late stage of Alzheimer's disease may also be called the "severe" or "advanced" stage. In this stage, the person living with Alzheimer's disease eventually becomes unable to communicate verbally or look after themselves. Nonverbal communication becomes more important. The person in the late stage of Alzheimer's disease will experience:

Severe impairment in memory, processing new information and recognizing time and place, Losing capacity for recognizable speech and The loss of the ability to eat, walk and use the toilet without assistance.[19]

Alzheimer's disease is most common in people over the age of 65, and affects slightly more women than men. The risk of Alzheimer's disease and other types of dementia increases with age, affecting an estimated 1 in 14 people over the age of 65 and 1 in every 6 people over the age of 80. However, around 1 in every 20 cases of Alzheimer's disease affects people aged 40 to 65.[20]

Etiology \Epidemiology

Alzheimer's disease is an unavoidable neurological disorder in which the death of brain cells causes memory loss and cognitive decline and ultimate dementia.[21]

These include:

Exacerbation of aging degeneration of anatomical pathways, including the cholinergic and corticocortical pathways environmental factor such as exposure to aluminum, head injury, or malnutrition genetic factors including mutations of amyloid precursor protein (APP) and presenilin (PSEN) genes and allelic variation in apolipoprotein E (Apo E), mitochondrial dysfunction, a compromised blood brain barrier, immune system dysfunction, and infectious agents. [22]

At present, the etiology of Alzheimer's disease (AD) is still unclear, but both genetic and non-genetic factors are thought to take part in the etiopathogenesis of AD. In the future, more high-quality and large-sample epidemiologic studies are needed to identify risk factors for AD, and the interaction models between genetic and nongenetic risk factors required further investigation.[23]

Dominant mutations have been identified, in the beta-amyloid precursor protein gene (APP), and in two homologous genes presenilin 1 (PSEN-1) and presenilin 2 (PSEN2). also It is clear that other yet unknown genes must be involved in the etiology of AD.[24]

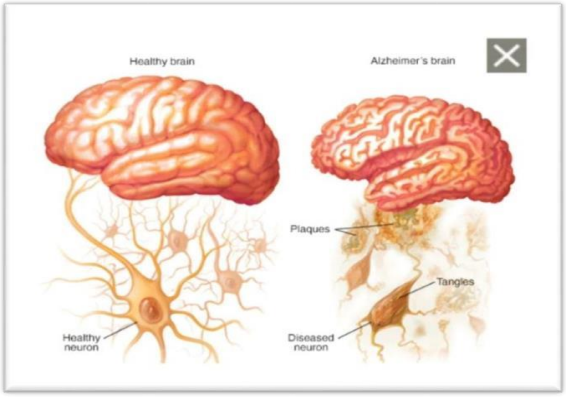

Figure .1)-Healthy brain and brain with Alzheimer's disease. In the brain of someone with Alzheimer's disease, amyloid plaques form and tau proteins change shape and become tangles.

Environment factor

Environmental risk factors might play an important role in decelerating or accelerating AD progression.

Some heavy metals have the capacity to enhance amyloid β (Aβ) peptide along with tau phosphorylation, initiating amyloid/senile plaques, as well as neurofibrillary tangle formation; therefore, neuronal cell death has been observed.

Theses heavy metal are as follows:

Among well-known environmental risk factors, prolonged exposure to several heavy metals, for example, aluminum, arsenic, cadmium, lead, and mercury; particulate air, and some pesticides as well as metal-containing nanoparticles have been participated to cause AD. Long term exposures to these environmental contaminants together with bioaccumulation over an individual's life-time are speculated to induce neuroinflammation and neuropathology paving the way for developing AD. [26]

Neurodegenerative disorders are typically sporadic in nature in addition to usually influenced through an extensive range of environmental factors, lifestyle, and genetic elements.[25]

Environmental factors possibly include inorganic and organic hazards, exposure to toxic metals (aluminium, copper), pesticides (organochlorine and organophosphate insecticides), industrial chemicals (flame retardants) and air pollutants (particulate matter).[26] Environmental exposures including toxins and nutrition may hamper the developing brain in utero, limiting the brain's reserve capacity and increasing the risk for Alzheimer's disease (AD).[27]

Risk Factors

In this context we focusing on early detection and better control of the most important risk factors, concomitantly with trying to find potentially protective factors that may delay the onset of AD.[29] These risk factors may act collectively to cause AD pathology: 1) by promoting the liberation of oxygen free radicals with age, 2) via environmental stress acting on regulatory genes early and later in life ('dual hit' hypothesis), or 3) by increasing the cumulative 'allostatic load' on the body over a lifetime.

As a consequence, life-style changes which reduce the impact of these factors may be necessary to lower the risk of AD.[28] potentially protective trait of caffeine in AD, while other data mainly from human studies lean toward no correlation or even suggesting that caffeine is a veritable risk factor for dementia.[29]

Risk factors for AD include aging, sex, lifestyle, comorbidities, and genetic factors. Considering the progressive aging of the population, the prevention or delay of cognitive dysfunction by targeting modifiable risk factors is becoming a therapeutic approach of growing interest.[30]

PATHOPHYSIOLOGY

AD is a complex, multifactorial, neurodegenerative disease, resulting from complicated interactions of one's genetic makeup, education, age, and environment.

[33] The pathophysiology of Alzheimer's disease (AD) is complex, involving several neurotransmitter systems and pathophysiologic processes.[31] Many hypotheses have laid the foundation to gain understanding of the etiology of the disease, with one of the oldest being the cholinergic hypothesis.[33]

Neuronal loss and/or pathology may be seen particularly in the hippocampus, amygdala, entorhinal cortex and the cortical association areas of the frontal, temporal and parietal cortices, but also with subcortical nuclei such as the serotonergic dorsal raphe, noradrenergic locus coeruleus, and the cholinergic basal nucleus.[32]

This hypothesis is based upon the fact that AD patients show reduction in activity of choline acetyltransferase and acetylcholinesterase in the cerebral cortex compared with the normal brain.[33] at postmortem and neurosurgical cerebral biopsy and the behavioural consequences of cholinomimetic drugs and cholinergic lesions. Such studies have resulted in the discovery of an association between a decline in learning and memory, and a deficit in excitatory amino acid (EAA) neurotransmission, together with important roles for the cholinergic system in attentional processing and as a modulator of EAA neurotransmission.[34]

The Tau hypothesis has also been proposed, considering AD histopathology reveals intraneuronal

neurofibrillary lesions made up of tau proteins and Tau proteins are mainly found in neurons and are involved in the assembly and stabilization of the neuronal microtubule network. Tau protein becomes pathological when the phosphorylation regulation becomes unchecked and hyper phosphorylated tau proteins polymerize into filaments and become neurofibrillary tangles.[33]

This leads to malfunction of the structural and regulatory actions of the cytoskeleton and then leads to abnormal morphology, axonal transport, and synaptic function of neurons, thus leading to neurodegeneration. [33]

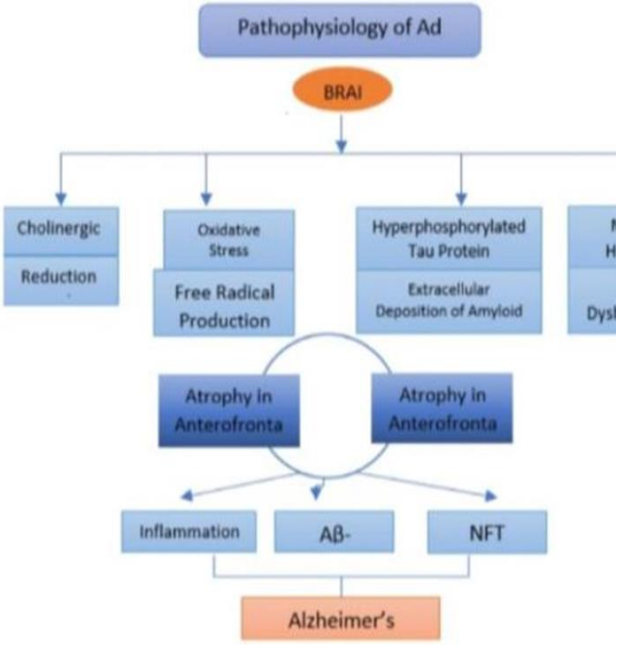

Figure 2:Pathophysiology of AD .[35]

DIAGNOSTIC TESTS

Early and accurate diagnosis of Alzheimer's disease (AD) has a major Impact on the progress of research on dementia.[36] There are three stages in developing clinically applicable Diagnostic tests or criteria for Alzheimer's Dementia.

The testing of single or individual diagnostic tests which may be laboratory based, clinical, genetic or radiological in nature.

Applying diagnostic test accuracy statistical enquiryon a battery or collection of the above tests (e.g., Devanand et al. akin to the development of the antenatal triple test for Down's Syndrome.

Consensus statement by clinical specialists using what the assembled and invited experts deem to be the most promising imaging, neuropsychological and laboratory tests. For example those described byTabert et al. and Dubois
et al. [37]

Diagnosing Alzheimer's disease would likely include the following tests:-

Physical and neurological exam

A health care provider will perform a physical exam. A neurological exam may include testing:

Reflexes, Muscle tone and strength, Ability to get up from a chair and walk across the room ,Sense of sight and hearing, Coordination, Balance.

Lab tests

Blood tests may help rule out other potential causes of memory loss and confusion, such as a thyroid disorder or vitamin levels that are too low. Blood tests also can measure levels of beta-amyloid protein and tau protein, but these tests aren't widely available and coverage may be limited.

Mental status and neuropsychological testing

Your provider may give you a brief mental status test to assess memory and other thinking skills. Longer forms of this type of test may provide more details about mental function that can be compared with people of a similar age and education level. These tests can help establish a diagnosis and serve as a starting point to track symptoms in the future.

Brain imaging

1) PET Scan

Pathologic species of two proteins, amyloid-β (Aβ) and hyperphosphorylated tau accumulate in the brains of persons with AD. PET scans are able to assess for both proteins and serve as a reliable biomarker. Amyloid accumulation precedes clinically significant cognitive changes and tau accumulation progresses in step with cognitive decline, suggesting the value of PET scans for diagnosis and measurement of disease progression .[38]

Fluorodeoxyglucose (FDG) PET imaging -Scans show areas of the brain in which nutrients are poorly metabolized.

Finding patterns in the areas of low metabolism can help distinguish between Alzheimer's disease and other types of dementia.

Amyloid PET imaging -Can measure the burden of amyloid deposits in the brain. This test is mainly used in research but may be used if a person has unusual or very early onset of dementia symptoms
Tau PET imaging
Which measures the tangles in the brain, is generally used in the research
setting.

2) Computerized tomography (CT).
a CT scan, a specialized X-ray technology, produces cross-sectional images of your
brain. It's usually used to rule out tumors, strokes and head injuries.

3) Magnetic resonance imaging (MRI).
MRI uses radio waves and a strong magnetic field to produce detailed images of the brain. While they may show shrinkage of some brain regions associated with Alzheimer's disease, MRI scans also rule out other conditions. An MRI is generally preferred to a CT scan to evaluate dementia.[37]
Early diagnosis and intervention to delay the onset of dementia are beneficial for patients and their carers and can result in substantial cost savings to healthcare systems. The positive benefits of receiving an early Alzheimer's disease diagnosis to the patient are that it provides an explanation for the symptoms and signs they are experiencing and puts an end to their suspicions .[39]

Prevention
The overall goal of primary prevention is to reduce the incidence of disease, by intervening before disease onset through promoting the initiation and maintenance of good health or eliminating potential causes of disease.[40]
primary prevention by acting on modifiable risk factors, the other is a pathophysiology-driven approach aimed to identify individuals in a preclinical stage of the disease and treating them with drugs purporting to act on molecular targets of the amyloid cascade.[41]
The aim of secondary prevention is to detect a disease early, when it is asymptomatic, and by treatment prevent it from progressing into a serious outcome. First, the disease has to have a preclinical phase that is possible to detect, it should be common enough to warrant a search for its latent stages, and the consequences of the untreated condition must be substantial.
There must be enough resources to do a diagnostic work-up in those patients with a positive screen. Finally, an effective therapy must exist that is more beneficial at the presymptomatic than at the symptomatic phase.[42]
In tertiary prevention of Alzheimer's we proposed the tertiary prevention strategy for AD Avoiding systemic diseases, sleep disorders and environmental risk factors, maintaining healthy diet and exercise, and preventing the production of Aβ at the preclinical stage should represent the primary methods for AD prevention.[43] Several promising trials with these approaches are currently ongoing and results are expected in the next few years.[41] Previous intervention efforts aimed at preventing dementia and AD focused on the management of single risk factors, with relatively modest findings. Also, the effect of risk factors depends on age at exposure, indicating that the timing of preventive interventions needs to be carefully considered.
In view of the complex multifactorial nature of AD, as well as its long pre-clinical (asymptomatic) phase, interventions simultaneously targeting multiple risk factors and disease mechanisms at an early stage of the disease are most likely to be effective.[44] Preventing or delaying the onset of cognitive impairment and AD will provide the greatest benefit to individuals and society by pushing the onset of disease into the later years of life.[45]

TREATMENT

Much of the research in AD in the last decade has been directed towards disease modifying therapy that will alter the course of the disease rather than act on symptoms alone, however the lack of effective disease-modifying drugs arising from these studies reflects the challenges involved in developing a therapeutic agent with potential to modify the course of a disease as complex as AD.[46]
Four approved medications comprising three, AChE inhibitors and Memantine are currently available to treat AD also, All AChE inhibitors (donepezil, Aricept® Rivastigmine, Exelon®; galantamine, Razadyne are indicated For the treatment of mild to moderate AD; in the US and Japan, Donepezil can be used for severe AD as well Tacrine (Cognex®) was

the first drug for the treatment of the Memory problems of AD approved by the FDA in 1993, but Was of limited clinical significance due to the potential of Severe side effects, in particular hepatoxicity also In the US, Tacrine Has been withdrawn from use in 2013, because of concerns on Safety and availability of other AChE with a better adverse Event profile and the un-competitive NMDA receptor antagonist Memantine (Namenda®) is indicated to treat moderate to Severe AD.[47] To date, only symptomatic treatments exist for this disease, all trying to counterbalance the neurotransmitter disturbance.[48]

CONCLUSION

AD is the most common of many causes of dementia, and its prevalence is increasing worldwide. Disease pathology starts years before noticeable symptoms. Neuropsychological, imaging, and spinal fluid tests can establish the diagnosis with high accuracy.

Although there are currently no treatments that slow the disease process, management of the cognitive and behavioral symptoms of AD dementia can significantly improve the lives of patients and their caregivers.

There is no perfect diagnostic test for AD, but neuropsychological testing, neuroimaging, and CSF analysis can substantially increase diagnostic accuracy. There is no cure for AD. Ideal AD management includes a combination of symptomatic treatment for cognitive issues, detection and judicious control of behavioral issues, and caregiver support.[49]

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