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A REVIEW ON ETIOLOGY AND TREATMENT OF ALZIEMER'S DISEASE

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ABSTRACT

Alzheimer's disease is a progressive and fatal neurodegenerative disorder manifested by cognitive and memory deterioration, progressive impairment of activities of daily living, and a variety of neuropsychiatric symptoms and behavioral disturbances. Prevalence studies suggest that in 2000 the number of persons with Alzheimer's disease in the United States was 4.5 million. The percentage of persons with Alzheimer's disease increases by a factor of two with approximately every five years of age, meaning that 1 percent of 60-year-olds and about 30 percent of 85-year-olds have the disease. Without advances in therapy, the number of symptomatic cases in the United States is predicted to rise to 12.7million by 2050. AD is clinically characterized by a global decline of cognitive function that progresses slowly and leaves. The earliest phase of Alzheimer's disease (cellular phase) happens in parallel with accumulating amyloid β, inducing the spread of tau pathology. The risk of Alzheimer's disease is 60–80% dependent on heritable factors, with more than 40. Alzheimer's disease-associated genetic risk loci already identified, of which the APOE alleles have the strongest association with the disease. Several approved drugs ameliorate some of the symptoms of Alzheimer's disease, but no current interventions can modify the underlying disease mechanisms. Management is focused on the support of the social networks surrounding the patient and the treatment of any co-morbid illnesses, such as cerebrovascular disease. Accurate diagnosis at an early stage is the need of the hour for initiation of therapy. The cause for most Alzheimer's cases still remains unknown except where genetic distinctions have been observed. Thus, a standard drug regimen ensues in every Alzheimer's patient, irrespective of the cause, which may not always be beneficial in halting or reversing the disease progression. To provide a better life to such patients by suppressing existing symptoms, early diagnosis, curative therapy, site-specific delivery of drugs, and application of hyphenated methods like artificial intelligence need to be brought into the main field of Alzheimer's therapeutic.

KEYWORDS: Alziemer, Etiology, Mechanism, Symptoms, Treatment, Therapy, Artificial Inteligence.

INTRODUCTION

Alzheimer's disease is the main cause of dementia and is quickly becoming one of the most expensive, lethal, and burdening diseases of this century.

Alzheimer's disease (AD) accounts for 60–80% of all cases of dementia worldwide. Alzheimer's Disease (AD) is the most common cause of dementia.

Alzheimer's disease is a progressive, unremitting, neuro degenerative disorder that affects wide areas of the cerebral cortex and hippocampus. Abnormalities are usually first detected in the brain tissue that involves the frontal and temporal lobes, and then slowly progress to other areas of the neocortex at rates that vary considerably between individuals . Alzheimer's disease is associated with the accumulation of insoluble forms of amyloid-β (Aβ) in plaques in extracellular spaces, as well as in the walls of blood vessels, and aggregation of the microtubule protein tau in neurofibrillary tangles in neurons.

Aβ is derived by the proteolytic cleavage of amyloid precursor protein (APP) by a complex family of enzymes (γ-secretases and β-secretases), which include presenilin 1 (PS1; encoded by PSEN1) and PS2.[1]

Dementia includes memory loss and difficulties with thinking, language and problem-solving skills. As per the WHO update, on epidemiology of AD in 2013, the number of people suffering from dementia worldwide is likely to triple by 2050 which was approximately 35.6 million in 2010. The incidence of dementia increases with age, approximately 5-8% are affected over age of 65, the number increases to 25-50% as the age rises over 85.

The prevalence of AD for men was lower than that for women by 19-29%.

China, USA, India, Japan, Germany, Russia, France and Brazil were the nine countries in descending order of incidence of people suffering from dementia , and the numbers more than 1 million (USFDA 2013).[2]

Medications used for treatment of NDs, including AD and Parkinson's disease, slow disease progression.

Cell therapy may be valuable strategy for the treatment of NDs; neural tissue can be repaired or healthy glial cells can be protected from further damage by replacing differentiated cells with stem cells.[3]

However, this method is constrained by its time- and labor-intensive nature.

Therefore, there is a compelling need for the development of highly efficient and cost- effective methods to facilitate nerve repair and regeneration.[4]

According to previous studies, vitamin B12 deficiency is associated with neurodegenerative disorders and increased risk of AD.[5]

Increased homocysteine levels are a specific indicator of vitamin B12 deficiency, and can cause brain damage through oxidative stress, increased calcium influx, and apoptosis.

Etiology

Alzheimer disease is characterized by gradual and progressive neurodegeneration caused by neuronal cell death.

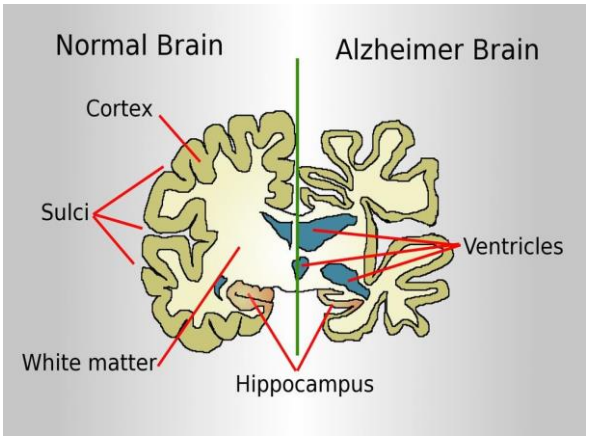
The neurodegenerative process typically begins in the entorhinal cortex within the hippocampus.

Genetic factors have been identified to contribute to both early and late-onset AD. Trisomy 21, for example, is a risk factor associated with early-onset dementia.

AD is a multifactorial condition associated with many known risk factors. The most significant factor is age,

with advancing age being the primary contributor.

The prevalence of AD approximately doubles with every 5 years increase in age.



Infectious Etiology of Alziemer's Disease

The importance of inflammatory processes in the pathogenesis of AD has also initiated research on the role of infectious agents in these reactions in the CNS.

In recent years, numerous studies have confirmed the relationship between different microbial infections, cognitive decline and AD. Systemic bacterial and viral infections, such as human herpesviruses, spirochetes, Chlamydia pneumoniae or Borrelia burgdorferi, may increase the inflammatory state and the susceptibility to development of AD.[6]

Pathogens possibly associated with the development of AD are presented in Table 1.

Pathogen
1. Viruses Human herpesvirus 1 (HHV-1) Human herpesvirus 2 (HHV-2) Cytomegalovirus (CMV), (HHV-3) Epstein-Barr virus (EBV), (HHV-4) Varicella-zoster virus (VZV), (HHV-5) Human herpesvirus 6 (HHV-6) Hepatitis C virus (HCV)
2. Bacteria Chlamydia pneumoniae Helicobacter pylori Borelia burgdorferi Treponema pallidum Porphyromonas gingivalis Fusobacterium nucleatum Prevotella intermedia and other periodontal bacteria
3. Fungi Candida albicans
4. Protozoa Toxoplasma gondii

1. Viral infections

One hypothesis about the development of AD blames the reactivation of latent infection of herpes simplex virus (HHV-1, Human herpesvirus 1). The concept of the viral,especially HHV-1, role in AD was proposed for the first time in 1982 by Ball.[7]

It was noted that damage of the brain tissue in the early stages of the disease includes the same areas, that are affected by the inflammation of the brain caused by HHV-1.[7]

Based on the presence of antibodies in the blood, it is estimated that about 80% of the population is infected with HHV-1. After the primary infection the virus turns into a latent state, and exists in the trigeminal ganglia.

Periodic reactivation of HHV-1 can be asymptomatic, unless the immune system is weakened, for example because of aging, stress, immunosuppression or peripheral infections.[8]

2. Bacterial Infections

More than a century ago, Alzheimer and his colleagues discussed the possibility that microorganisms may be involved in the formation of senile plaques.[9]

Currently the important role of infections in AD etiology is postulated by many research teams.

Chronic spirochetal infections are responsible for syphilitic dementia in the atrophic form of general paresis, and it was noted in the past that clinical and pathological hallmarks of the disease are similar to those observed in AD. It is well known that spirochetes are neurotropic pathogens.[10]

These bacteria infect the brain and pass into latent infection. In addition to hematogenous dissemination, spirochetes can spread via the lymphatics and along nerve fiber tracts; e.g., periodontal invasive spirochetes can invade and transmit along the trigeminal nerve and trigeminal ganglia.

3. Fungal Infections

Recently, fungal infections in AD patients have gained much attention.[11]

Alonso and colleagues detected fungal proteins in CSF from AD patients by using different anti- fungal antibodies.[11]

Fungal DNA and proteins were also found in frozen brain tissue from AD patients, but not from control patient tissue

Fungal material was detected both intra-and extracellularly using specific antibodies against several fungi: Candida famata, C. albicans, C. glabrata, Phoma betae, and Syncephalastrum racemosum.

Fungal material was found in particular brain regions including the external frontal cortex, entorhinal cortex/hippocampus, cerebellar hemisphere, and choroid plexus. Detailed analysis of brain sections derived from AD patients showed that all were infected with fungi.[12]

Enornmental Factors in Etiology

The proposition that environmental agents, such as diet, aluminum, and viruses, are as important as genetic factors in the etiology of Alzheimer's disease (AD).

Diet, dietary fat, and to a lesser extent, total energy (caloric intake), were found to be significant risk factors for the development of AD in a dozen countries, while fish consumption was found to be a significant risk reduction factor.

An acid-forming diet, such as one high in dietary fat or total energy, can lead to increased serum and brain concentrations of aluminum and transition metal ions, which are implicated in oxidative stress potentially leading to the neurological damage characteristic of AD. Many of the risk factors for AD, such as cholesterol and fat, and risk reduction factors, such as whole grain cereals and vegetables, are shared with ischemic heart disease. Aluminum may cause neurological damage and a number of studies have linked aluminum to an increased risk for developing AD.[13]

Sign and Symptoms

The general symptoms are

- Inability to communicate.
- No awareness of recent experiences or surroundings.
- Weight loss with little interest in eating.
- Seizures.
- General physical decline, including dental, skin, and foot problems.
- Difficulty swallowing.
- Groaning, moaning, or grunting.
- Increased sleeping.

Cognitive symptoms

Impaired memory is the hallmark of the cognitive presentation of AD. The initial phase is characterized by subtle memory deficits (e.g., misplacing objects, forgetting conversations, problems remembering names, and missing appointments). However, AD patients usually have a global cognitive impairment (Becker 1994a, Cahn 1997). A study conducted to identify the best predictors of AD found that auditory verbal and visual delayed recall.

Neuroloical signs

The general neurological examination in AD, especially early in the course, is normal. In fact, localizing signs should prompt a careful search for other etiologies. Localizing signs in the presence of a clinical picture that looks much like AD suggest that two processes are extant. Non-specific neurological signs (e.g., frontal release signs), cranial nerve abnormalities (e.g., diminished upward gaze), and gait abnormalities are more frequent in AD than in normal aging.

Behavioral and psychological symptoms

Psychotic symptoms (e.g., delusions, hallucinations), and disruptive behaviors (e.g., aggressive behavior, psychomotor agitation, wandering) are common in AD patients.

These may represent specific phenotypes with different natural histories.[14]

Mechanism of AD

Numerous hypotheses have been proposed to unravel the pathogenesis of AD, yet a unified theory remains elusive, likely due to the complex nature of AD. AD can be categorized into two main types: familial (accounting for 1-5% of AD cases) and sporadic forms (over 95% of cases).

Familial AD (FAD) is predominantly characterized by autosomal dominant genetic mutations in amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) genes, typically manifesting between 30-65 years and progressing rapidly. In contrast, sporadic AD (SAD), also known as late-onset AD, usually manifests after the age of 65 and is influenced by a combination of genetic risks, environmental factors, and various comorbidities. Genome-wide association studies (GWAS) and genome-wide meta-analyses have identified numerous genetic risk loci associated with SAD, implicating pathways in immune response, lipid metabolism, Aβ plaque, NFTs, and endocytosis, yet many loci remain undiscovered.

Non-genetic factors such as lifestyles, psychosocial factors, environment, and diseases related to AD (comorbidities and complications), may elevate the risk of developing AD. They may achieve this by altering biological pathways and genetic susceptibility, making it challenging to pinpoint a direct cause of clinical pathology in AD.

Furthermore, different AD subtypes (typical and atypical) often exhibit various clinical symptoms.
Thirdly, AD has multiple pathological features including AβPlaques, NFTs, synaptic and neuronal loss, and neuroinflammation.

Overall, the diversity of triggers, clinical manifestations and neuropathological features underlie the heterogeneity of AD.

Consequently, developing a comprehensive theoretical framework that links genetic foundations, molecular mechanisms, and clinical phenotypes of AD is extremely challenging. Current limitations in AD research also hinder our comprehensive understanding of its pathophysiology.

Moreover, the high failure rate of clinical trials makes it difficult to effectively validate hypotheses, possibly attributed to the coexistence of multiple theories (which will be detailed in subsequent sections).[15]

Diagnostic Criteria

The diagnosis of Alzheimer's disease has gone from a purely pathological one, in the days of Alois Alzheimer (1864–1915) to a clinical, exclusionary approach in 1984.

The clinical diagnosis was based on the criteria defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, via a combined clinical and biological approach developeped by the International Working Group and subsequent efforts by the National Institute on Aging and the Alzheimer's Association working groups, incorporating biomarkers to make the categorisation of Alzheimer's disease purely biological. Initially, the diagnosis of Alzheimer's disease was restricted to the stage of dementia, a clinical syndrome characterised by substantial progressive cognitive impairment affecting several domains, or neurobehavioral symptoms of enough severity to cause evident functional impact on daily life.

A person with dementia is no longer fully independent, and this loss of independence is the primary feature differentiating dementia from mild cognitive impairment.[16]

Treatment of AD

Disease-modifying treatments, i.e. those proven to alter the underlying disease pathology or disease course, are not yet available. Optimal management needs to be tailored to the individual patient and their specific circumstances, and to adapt as the disease progresses.

Both the patient and carers should be involved in decision-making, with all reasonable steps taken to allow for patient involvement even as cognition declines; a multi-disciplinary approach including medical professionals,nurses, social services and charities/support services is vital.

Important issue to consider include driving, noting that a diagnosis of AD does not necessarily preclude driving if symptoms are mild and executive and parietal functions are relatively preserved; support at home; finances; and future

planning especially while the individual has capacity to make decisions.

Referral to palliative care to discuss end of-life planning can be particularly valuable, ideally in advance of end-stage dementia.

Acetyl-cholinesterase inhibitors (AChEI) (donepezil, galantamine and rivastigmine) are the mainstay of symptomatic treatment, increasing acetylcholine availability by inhibiting its breakdown in the synapse. Peripheral cholinergic side effects such as leg cramps and gastro- intestinal upset are common but usually well tolerated, especially when the drugs are introduced at low dose and titrated slowly.

AChEI should be avoided or used with caution in individuals with heart conduction defect due to the risk of brady-arrhythmias. AChEI have proven beneficial effects in mild to severe AD, with most evidence at the mild-to-moderate stage.[17] Differences in the frequency of dosing, dose variation, timing of escalation, and delivery (oral and transdermal) provide options that can be tailored to individual patients. The DOMINO-AD study demonstrated that withdrawal of donepezil in moderate-severe AD increased the risk of nursing home placement in the following 12 months of treatment, but not in the following three years withdrawal of treatment may have potential risks, even when the benefits of continuing are not clear.[18]

Memantine is an alternative symptomatic treatment, licenced for moderate-severe AD. Memantine, a low affinity NMDA receptor antagonist, aims to reduce L- glutamate excitatory neurotoxicity without interfering with its physiological actions.

Side effects include constipation and headache. Memantine has been shown to have a small but clinically appreciable benefit on cognition and functional decline in patients with moderate-severe AD, with some evidence it reduces the likelihood of patients developing agitation.[19]

Advancement in Blood BioMarkers

Recently, a biological rather than a syndromic definition of the disease has been proposed that is based on biomarkers that reflect neuropathological changes. In AD, there are two main biomarker categories, namely neuroimaging and fluid biomarkers [cerebrospinal fluid (CSF) and blood].

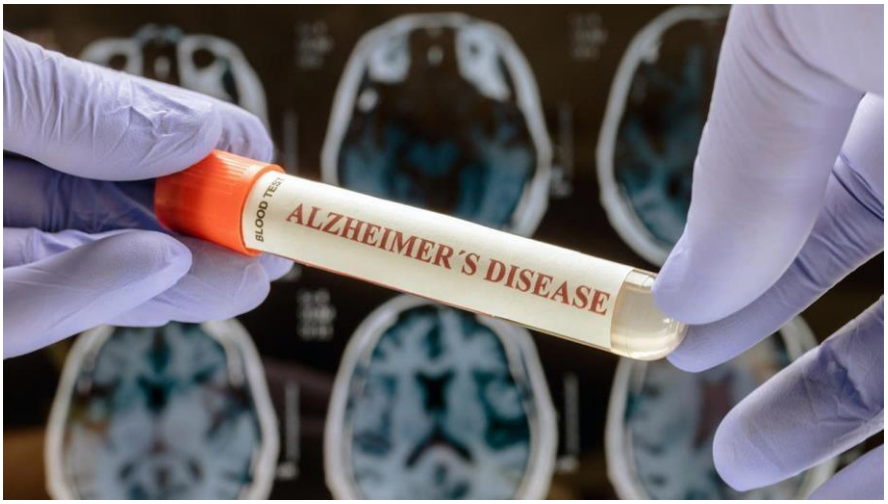
As a complex and multifactorial disease, AD biomarkers are important for an accurate diagnosis and to stage the disease, assess the prognosis, test target engagement, and measure the response to treatment.

In addition, biomarkers provide us with information that, even if it does not have a current clinical use, helps us to understand the mechanisms of the disease. In addition to the pathological hallmarks of AD, which include amyloid-β and tau deposition, there are multiple concomitant pathological events that play a key role in the disease.

These include but are not limited to, neurodegeneration, inflammation, vascular dysregulation or synaptic dysfunction. In addition, AD patients often have an accumulation of other proteins including α-synuclein and TDP-43, which may have a pathogenic effect on AD. In combination, there is a need to have biomarkers that reflect different aspects of AD pathogenesis and this will be important in the future to establish what are the most suitable applications for each of these AD-related biomarkers

It is unclear whether sex, gender, or both have an effect on the causes of AD.

There may be differences in fluid biomarkers due to sex but this issue has often been neglected and warrants further research.[20]



Newest Stratagies in Early Detection of AD Biomarkers

A biomarker is an indicator considered for evaluation of any normal biological as well as pathogenic processes and pharmacological effects of any therapy. In the case of AD, a biomarker can be used to assess the overall health and dis eased condition of aged patients.[21]

An extracellular deposition of amyloid-β (Aβ) protein and aggregated form of hyper phosphorylated tau protein in the brain are two main pathological characteristics of AD.[22]

Recently all the important molecular biomarkers of Alzheimer's disease were critically discussed for their status and prospects.[23]

Cerebrospinal Fluid (CSF) Proteins

More specific to AD, CSF measures of Aβ1-42, t-tau, and p-tau and molecular imaging using PET have become widely adopted with improving assays and ligands. Some of the previous studies carried out in vitro and human trials have indicated the role of non-essential heavy metals cadmium (Cd), mercury (Hg), lead (Pb), and arsenic (As) in causing Aβ protein aggregation along with worrisome levels of tau hyper phosphorylation.[24]

Brain Derived Neurotrophic Factor (BDNF)

The decline in memory with the reduction in hippocampal volume (HV) corresponding with high Aβ levels has been already reported in healthy individuals; Lim et al.(2013) showed that BDNF Val66Met worsens these conditions more in the preclinical stage of AD.[25]

Current Stratagies in the Treatment of AD

1. Gene Therapy

Gene therapy interventions are aimed to tackle a disease at its source, mostly a faulty DNA/gene/protein, to repair it and allow the cells to fix the problem. After revealing various genes involved in Alzheimer's pathology, it opens upvast avenues for gene therapy, which involves inserting new genetic material into living cells using viruses. Due to the

recent developments in gene therapy associated approaches in recombinant adeno-associated viruses (rAAVs), the possibility for treating these diseases in human beings is foreseen. In an effort to test the ability to degenerate neurons in AD towards a nervous system growth factor (NGF), Tuszynski etal. (2015) subjected ten patients with early AD with NGFgene ex vivo or in vivo therapy.[26]

Immunotherapy for Alzheimer

Various mechanisms have been hypothesized for Aβ immunotherapy. The soluble equilibrium mechanism includes antibodies neutralising and solubilising the Aβ plaque both centrally and peripherally. Phagocytosis mechanism is base on opsonisation of Aβ plaque which stimulates microglia associated phagocytosis. Antibodies also bind to Amyloid seed in the initial stages and can prevent its propagation.[27] There are several other mechanisms like direct method (in which Aβ plaque are unbundled) and peripheral sink mechanism (removal of Aβ from the brain to plasma).[28]

2. Metal Chelators

Interaction of metals with Aβ leads to the generation of ROS as well as abnormal metal ion homeostasis which is linked to the pathogenesis of AD. Metal chelators are agents that break the Aβ-metal complex and restore metal ion homeostasis and hence reduce neuro toxicity. Chelators usually have low molecular weight, small molecular size and neutral or low charge to penetrate blood brain barrier. Chelators do not exhibit strong specific activity towards metal ions as it can deplete its level and lead to abnormal metal ion concentration.[29]

Future Directions in Prediction of Alziemer's Disease with Artificial Inteligence

The field of bioscience has undergone an exponential expansion with recent advances in the field of genomics, proteomics, transcriptomics, epigenomics, metagenomics and metabolomics etc.

These developments in the field have offered huge amount of unprocessed data, which called for the unprecented rise of Artificial intelligence (AI) to use and process abundant imaging data with computer-controlled robot and information technology.

AI is able to integrate the accumulated data and to generate valuable predictions for therapeutic applications. As it's impossible to conclude one particular gene for a disease, the recent failure of a BACE1 inhibitor for Alzheimer's has drawn attention towards the distinctive role of multiple genes in pertinent biological pathways and the importance of data reproducibility to address serious issues in this field.

AI has capacity to process a massive amount of wholgenome data to recognize the most relevant pathways, and increase the probability to find the best target for the therapy. These studies have identified non-coding regions like THAP9-AS1 as the topmost targets for AD. These targets could potentially answer more fundamental questions about memories in the future.[30]

The advantage of AI is the algorithm can be applied to many disparate and unassociated data sets. An early detection has become a prerequisite for the betterment of AD. By the time the clinical symptoms become evident, the neurons are already dead and the condition is impossible to reverse. McGill University's department of psychiatry is using public data from about 800 individuals from normal control, Alzheimer's patients or the ones suffering from mild cognitive impairment. AI interface is using their MRI scans, a highly associated genetic marker in AD, and a simple cognition activity profile to identify patients with decline signs despite the diagnosis. Efforts are being made to test if the tool can

be used advanced for clinical set-up, as data can remain useful even after many years since it is first collected for prediction of neurodegeneration over time in the individuals. With the advent of AI, doctors are hopeful to get certainty to judge the risk for decline in elderly or middle aged subjects.[31]

Other approaches included building a Neuroimaging

Identification system with the help of Git Bash programming aid software, Inception V3 image sorter and Unix commands. MRI of 2542 patients diagnosed with Alzheimer and 500 MRI of healthy patients from ADNI (Alzheimer disease Neuroimaging Initiative) were used. Hippocampal atrophy and volumetric reduction of entorhinal cortex were mainly analysed by the system to differentiai AD and healthy patients.

To perform this analysis, the photos of the brain scan were uploaded and then segregated into pixels. The colours of the pixel were examined and bottlenecks, text files were created which were reviewed 3 million times. Then the results were generated in descending order of possibilities differentiating between AD and healthy with good accuracy.[32]

MATERIAL AND METHODS

Materials and methods for Alzheimer's disease research can include:

- **Imaging techniques:** These include positron emission tomography (PET) and functional MRI (fMRI). PET and fMRI are functional techniques that can detect chemical or cellular changes linked to diseases.
- **Patient-oriented research:** This involves examining patients, taking family histories, administering memory tests, and using imaging to examine the brain.
- **Biomarker tests:** These include measuring amyloid and tau proteins in the fluid that surrounds the brain and spinal cord, or in the blood.

Chemicals and Reagents

Amyloid-beta (Aβ) peptides for aggregation studies. Tau proteins or phosphorylation-specific antibodies. Drugs or small molecules for therapeutic testing.

CONCLUSION

Dementia is a syndrome characterized by functional and cognitive decline. Various hypotheses, however unable to explain the complete picture, have been put forth for the pathogenesis of AD. The cause in many cases remains untraceable, hence no treatment options can halt or reverse disease progression, although some may temporarily ameliorate symptoms.

Gene therapy and Quantum dots are the recent additions as therapeutic agents for AD, however they are yet to be clinically approved. Early diagnosis is of utmost importance since it not only benefits the patient by providing prompt treatment but also aids in the inclusion of patients in the initial stages of the disease for the conduct of clinical trials of promising drug candidates.

Detection of AD with cerebrospinal fluid markers, blood test for inflammatory biomarkers, amyloid imaging with concurrent markers, volumetric MRI, are promising diagnostic indicators. As early diagnosis allows an access to treatment options and cost-effective caregiving.

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