



Recent Advancements In Understanding, Diagnosis & Therapeutic Approach Of Alzheimer's Disease.

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ABSTRACTS :

Alzheimer's disease (AD) is a multifactorial, polygenic neurodegenerative condition that, despite years of research and development, still does not have a cure. Some symptomatic therapies exist to address psychological symptoms, but none of these medications can stop the advancement of the disease. Moreover, in recent years, several anti-AD drugs have not succeeded in the final phases of clinical trials, resulting in multiple theories to account for these failures, such as an unclear understanding of disease pathways and mechanisms. Lately, several epigenetic factors have been associated with the pathogenesis of AD; therefore, they may act as potential diagnostic biomarkers for AD. Moreover, network biology methods have been suggested as valuable instruments to analyze AD at the systems level and identify multi-target-directed ligands as innovative therapies for AD. In this article, we present a thorough examination of Alzheimer's disease pathophysiology to improve comprehension of disease pathogenesis theories and to clarify the impact of genetic and epigenetic factors on disease onset and advancement. We likewise provide a summary of disease biomarkers and drug targets, proposing network biology methods as innovative tools for discovering new biomarkers and drugs. We suggest that utilizing machine learning and artificial intelligence for analyzing multi-omics data related to Alzheimer's disease will enhance drug and biomarker discovery initiatives, resulting in successful personalized anti-Alzheimer therapies.

KEYWORDS : Alzheimer's Disease, Diagnosis, Approach ,Biomarkers, Genetics, Pathogenesis, Treatments.

INTRODUCTION :

The criteria for clinically diagnosing Alzheimer's disease (AD) were established in 1984 by the Alzheimer's Disease and Related Disorders Association (ADRDA) workgroup and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS(1)). The NIA and AA proposed the ATN research framework in 2018 as a means of characterising and diagnosing Alzheimer's disease. Participants in these consultation meetings came from corporations and educational institutions, including representatives from many nations. During the advisory sessions, it was decided to form three separate workgroups that would be supervised by the Alzheimer's Association and the NIA. The task of developing criteria for identifying the dementia stage of Alzheimer's disease was assigned to one team(1,2)

The latest figures are alarming, with approximately 6 million Americans currently suffering from AD, leading to annual care costs estimated at \$305 billion, both directly and indirectly. Various factors such as genes, epigenetics, biology, and the environment interact with each other in the development of Alzheimer's disease. Nevertheless, genetic studies have shown that no specific gene can be identified as the sole potential target for AD development. Actually, disease development is influenced by various genetic and non-genetic factors.(3)

Other Factors Affecting Disease Pathogenesis

Neuronal damage can be observed mainly in the hippocampus, amygdala, and entorhinal cortex, as well as the association regions of the frontal, temporal, and parietal cortices, along with subcortical structures like the serotonergic dorsal raphe, noradrenergic locus coeruleus, and cholinergic basal nucleus.(4)AD is brought on by a confluence of environmental and genetic variables, and the environment cannot be disregarded. Much work has gone into finding those particular genetic and environmental components, assessing their relative significance, comprehending how they interact, and using this information to treat and prevent the illness. Age is one of the most significant risk factors for cognitive decline and AD among the other demographic characteristics, including gender, race, and socioeconomic status, according to numerous epidemiological studies, including those cited by Henderson . The prevalence of AD rises with age, reaching an estimated 19% in people aged 65 and 30–35%, potentially reaching 50%, in people aged 85 and above .(4,5)

Alzheimer's Disease Classifications

AD is typically categorized based on two factors: age and genetics (Table 1). AD is categorized into two main forms, depending on age: LOAD and EOAD. LOAD usually manifests in individuals who are 65 years old or older, even though the degenerative process can start affecting the brain up to 20

years before any signs show up. (6)The suggested system consists of three primary components: preprocessing, feature extraction, and disease classification.(7)

Voting layer

Because the diverse nature of the seven groups of attributes makes it challenging for a single classifier to effectively utilize multisource information, achieving satisfactory performance in the classification of AD remains difficult, regardless of the quantity of data available.(8)

Stacking layer

Stacking is an ensemble method where the outputs of several predictive models are integrated using another learning model to produce a final result. In our stacking layer, the outputs from the base classifiers in the voting layer serve as inputs to the Deep Belief Network (DBN), which consists of two Restricted Boltzmann Machines (RBMs).(8,9)

Table 1. Main types of Alzheimer's disease based on age and heredity.

Classification	Genetic Factors	Age Onset	Clinical Features	Risk Factors	Top Treatments
Early-onset	Yes	40s-50s	Plaques of amyloid and tau proteins	Family history	Acetylcholinesterase inhibitors(Donepezil,Galantamine, and Rivastigmine)
Late-onset	Yes (APOE	≥65	APOE) ε4 allele	Age ≥ 65 years,genetic and environmental factors	Acetylcholinesterase inhibitors (Donepezil,Galantamine, and Rivastigmine) and treatment of vascular risk factors and sleep and mood disorders.
Familial	Yes (PSEN1, PSEN2, APP)	40s–50s	Mutations in PSEN1, PSEN2,and APP	Family history	Acetylcholinesterase inhibitors (Donepezil,Galantamine, and Rivastigmine)

Alzheimer's Disease Diagnosis

AD is a condition that requires two criteria for diagnosis: a clinical phenotype involving symptoms like memory impairment, and neurological changes in the brain like NFTs and Aβ plaques. Clinical diagnosis of AD heavily relies on observing behaviors that align with known clinical features and ruling out other causes, as NFTs and Aβ plaques can only be identified post-mortem(11). In the last 15 years, significant advancements have been made in creating and making in vivo Alzheimer's disease biomarkers more accessible, understanding the disease's natural progression, and incorporating this information into diagnostic research. The discovery that CSF biomarkers enhanced the diagnostic precision and predictive capacity of MRI findings. Afterwards, a mixed classifier chose regions of interest in MRI and fluorodeoxyglucose PET scans, and when combined with CSF biomarker data, showed great accuracy.(10,11,12)

Alzheimer's Disease Biomarkers

Biomarkers play a crucial role in the precise identification of numerous diseases, including AD. While there have been recent improvements in diagnostic techniques for Alzheimer's disease, it is still difficult to distinguish Alzheimer's dementia from other types of dementia (15). Examining Aβ-42, total tau protein, and phosphorylated tau (p-tau) levels in cerebrospinal fluid (CSF) is now widely accepted as the most reliable biological indicator for diagnosing AD and distinguishing it from mild cognitive impairment and other forms of dementia. ADNI data have been utilized in a wide range of scientific disciplines, with 600 publications covering areas such as epidemiology, computer science, genetics, and more. Two initial studies identified a biomarker "signature" for AD, establishing specific levels of CSF biomarkers that indicate a high likelihood of the disease.(14 ,16)

Anti-Alzheimer's Drugs

Acetylcholine (Ach) is thought to be one of the main neurotransmitters in the brain. Cholinergic impairments that arise as Alzheimer's disease (AD) progresses might result in widespread cognitive dysfunction and decline. Genetic studies indicate that the production of amyloid β peptide is a crucial factor in the development of Alzheimer's disease (AD) (17). The way this peptide triggers neurodegeneration might be linked to inflammatory processes.Inflammation, a shared factor among various neurodegenerative diseases, has recently been recognized as a key mechanism driving the ongoing progression of neurodegeneration.(19)

Exploring Epigenetic Treatments

Epigenetics involves changes in DNA that can be inherited and acquired, influencing gene expression and function without altering the nucleotide sequence of the DNA.(18) Such modifications encompass DNA methylation and hydroxymethylation, various histone modifications, and the regulation of non-coding RNA. Histone modifications include processes like acetylation, methylation, crotonylation, ubiquitination, sumoylation, phosphorylation, hydroxylation, and proline isomerization.(20)

Epigenetics might clarify the influence of non-genetic factors in Alzheimer's disease (AD) and enhance our understanding of its causes. The term epigenetics was first coined by Conrad Waddington in the 1940s and is now defined as the investigation of the molecules and processes that maintain different states of gene activity without altering the DNA sequence.(21) More specifically, epigenetics encompasses DNA methylation and hydroxymethylation, modifications to histones, and the regulation of non-coding RNAs. (22)

Genetic Treatments

Alzheimer's disease (AD) is a significant health issue that imposes a substantial financial burden on society and consumes considerable medical and social resources. Caring for patients with AD involves a complex and multidisciplinary approach. (24) More than 90% of these patients have additional health conditions and need tailored treatment plans to minimize adverse drug reactions (ADRs), drug-drug interactions (DDIs), and avoid unnecessary expenses. The clinical application of pharmacogenetics in Alzheimer's disease (AD) is currently limited to acetylcholinesterase inhibitors (AChEIs) and memantine. Nevertheless, pharmacogenetic approaches ought to be implemented for emerging therapeutic strategies in AD, encompassing new AChEIs, neurotransmitter modulators, anti-amyloid beta (anti-A β) therapies, anti-tau treatments, multifunctional agents, epigenetic medications, and combination therapies.(23,25)

Special Considerations for Clinical Trials

Factors to be taken into account in the design of a clinical trial consist of trial justification, desired outcomes, statistical analysis method, sample size and enrollment, and interim monitoring (39)]. Typical clinical trial designs include single-arm trials, placebo-controlled trials, crossover trials, and factorial trials (35). Infrastructure and technology, cultures and languages, regulatory and reimbursement issues, academia and industry harmonization, availability, and access are identified as the main obstacles hindering successful clinical trials in the field of Alzheimer's disease (29). NLM's ClinicalTrials.gov Beta stated that 109 clinical trials connected to AD were ended over the past decade [13]. Trials for Alzheimer's disease were stopped for various reasons: lack of funding, COVID-19 restrictions on visits, difficulties with enrollment feasibility, safety concerns, slow recruitment of eligible participants, inadequate study design to meet trial goals, new data on safety or efficacy from other studies, unfavourable risk-benefit balance, and incorrect dosage settings. However, the recruitment of patients continues to be the main factor in determining the success of AD clinical trials. Hence, innovative clinical trial designs are necessary to speed up the approval process for registering new potential treatments or prevention methods for Alzheimer's disease. Nevertheless, new research methods must undergo thorough validation before being used in clinical trials (27,30, 33)

CONCLUSION :

AD is a disease caused by multiple factors and genetic traits. It is essential to develop new biomarkers for diagnosing diseases and treatments that can modify the disease's progression in order to slow down or stop the disease, decrease abnormal behaviors, and enhance cognitive function in patients with Alzheimer's disease (34). Recent developments in network biology strategies, combined with improvements in clinical trial planning and protocols, as well as the presence of robust machine learning and artificial intelligence algorithms, hold potential in discovering novel diagnostic biomarkers, enhanced drug targets, and efficient disease-modifying medications. This review offers a thorough look at Alzheimer's disease, focusing on popular theories about its cause, current treatments, and ongoing drug research initiatives.(40) We also emphasize new scientific proof linking epigenetic mechanisms and the microbiome to AD development and advancement. We suggest that utilizing AI and ML methods to analyze AD network biology data, such as genetic, transcriptomic, epigenetic, and metagenomic data, has the potential to transform our comprehension of disease pathways and enable the identification of novel biomarkers and drug targets. In the end, these researches will enhance our likelihood of finding approved diagnostic biomarkers and successful disease-altering treatments. Hence, there is a higher chance of important advancements in AD research occurring soon. This review summarizes current theories on AD development, as well as recent progress in identifying disease biomarkers and drug targets. It also offers details on AD medications in various development phases and showcases technologies predicted to speed up AD drug and biomarker findings.(32,36)

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