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REVIEW ARTICLE

Diagnosis and Treatment of Alzheimer's Disease Targeting the Amyloid Beta (Aβ)

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ABSTRACT: Alzheimer's disease (AD) is a major public health challenge, with its prevalence expected to rise dramatically in the coming years. The amyloid hypothesis suggests that amyloid beta (Aβ) plays a key role in the pathophysiology of AD, causing neuronal dysfunction and cognitive decline. This review provides an overview of recent advances in the diagnosis and treatment of AD, with emphasis on the role of Aβ. Diagnostic criteria for AD have evolved to include clinical biomarkers such as brain amyloid markers detected by positron emission tomography (PET) and cerebrospinal fluid (CSF) analysis. Emerging research suggests that retinal hyperspectral imaging may be a promising non-invasive biomarker of brain Aβ status. While current therapeutic options for AD are primarily focused on symptomatic relief, there is growing interest in disease-modifying treatments (DMTs) aimed at modulating Aβ pathology to alter the disease trajectory. Aducanumab, the first FDA-approved disease-modifying therapy for AD, represents a significant breakthrough in this regard. Other monoclonal antibodies targeting Aβ, such as Donanemab, Lecanemab, and Gantenerumab, are currently being studied in clinical trials. The integration of novel diagnostic approaches and disease-modifying therapies targeting Aβ pathology holds the promise of improving patient outcomes and reducing the societal burden of AD.

KEYWORDS: Biomedical and Health Sciences, Genetics and Molecular Biology of Disease, Alzheimer's Disease, Amyloid Beta, Hyperspectral Imaging.

Introduction

Alzheimer's disease (named after the German psychiatrist Alois Alzheimer), the most prevalent form of dementia, is a complex neurological disorder characterized by progressive cognitive decline. As of 2020, there are approximately 50 million AD patients worldwide, which is expected to double every 20 years to reach 152 million by 2050. AD also imposes a significant economic burden, with annual global costs estimated at 1 trillion USD. The multifactorial nature of Alzheimer's disease, involving genetic, environmental, and lifestyle factors, complicates its prevention and diagnosis. Regarding the currently unclear pathogenesis of AD, two hypotheses have been proposed: the cholinergic hypothesis and the amyloid hypothesis.[1] The 'amyloid hypothesis' states that amyloid beta (Aβ), a polypeptide derived from incorrect proteolytic cleavage in the brain, plays an important role in the origin and progression of the neurodegenerative disease.

Pathologically, AD is associated with Aβ deposition, subsequent formation of amyloid plaques outside neurons, and the intraneuronal accumulation of hyperphosphorylated tau proteins. Both abnormalities have been observed to induce neuronal apoptosis and ultimately lead to dementia,[2,3] although the exact mechanisms remain unclear. Aβ deposition is typically followed by synaptic dysfunction, tau protein abnormality in the cerebrospinal fluid (CSF), brain structural changes, and cognitive decline.[3,4] The accumulation of Aβ is asymptomatic and begins in the early stages of AD.[2] Recognizing Aβ as a potential biomarker for AD, many studies have been conducted to distinguish AD from normal individuals and to predict the progression or onset of AD by monitoring Aβ. The use of biomarkers for early diagnosis in preclinical stages or mild cognitive impairment holds promise to prevent or delay the progression of AD.[3,5]

Current advances in positron emission tomography (PET) imaging using Aβ-selective tracers have great utility in confirming the clinical diagnosis of the disease.[6] Since there is a substantial delay between the onset of cognitive impairment and the diagnosis of AD typically,[7,8] there is a strong need for practical, non-invasive, and cost-effective biomarkers to identify individuals at risk for AD.[9]

Current therapeutic options for AD are limited to medications that provide modest symptomatic improvement. As the amyloid beta(Aβ) is central to pathogenesis, Aβ-targeted immunotherapy has become a focus of attention as a putative disease-modifying treatment for AD.[10]

This review provides an overview of recent research findings on brain Aβ biomarkers and Aβ-directed immunotherapies in the context of AD diagnosis and treatment. This article highlights promising avenues to improve AD diagnostic accessibility and disease management by summarizing the latest findings.

Discussion

Amyloid beta pathology in AD:

The pathological characteristics of AD are linked to Aβ deposition, amyloid plaque formation outside neurons, and the accumulation of hyperphosphorylated tau protein within neurons. These proteins are known to induce neuronal apoptosis and ultimately lead to dementia.[2,3] The accumulation of Aβ starts in the early stages of the disease when no symptoms are

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present.[3] Studies incorporate early biomarkers to distinguish AD from normal individuals in an attempt to predict the progression or onset of AD from mild cognitive impairment or preclinical stages and to prevent disease progression.[3,5]

Found in the brain of patients with AD, Aβ is a peptide of 36-43 amino acids and becomes neurotoxic when it forms plaques. Aβ originates from amyloid precursor protein (APP), a transmembrane glycoprotein abundant in the central nervous system (CNS). APP is processed by two alternative pathways: the non-amyloidogenic and amyloidogenic pathways. The non-amyloidogenic path is a natural APP metabolism process that precludes Aβ formation. First, APP is cleaved by α-secretase within the Aβ domain, generating soluble α-APP fragments (sAPPα) and C-terminal fragment α (CTFα, C83); C83 is then cleaved by γ-secretase, which produces non-toxic P3 and AICD fragments. In the amyloidogenic pathway, APP is firstly cleaved by β-secretase, producing soluble β-APP fragments (sAPPβ) and C-terminal β fragments (CTFβ, C99). Subsequently, C99 is cleaved by γ-secretase, generating APP intracellular domain (AICD), and Aβ.[11,12] Aβ is converted to amyloid fibrils via a nucleation reaction, accumulating and coagulating.[3,13] Amyloid plaques, consisting primarily of amyloid fibrils, are surrounded by axons, dendrites, reactive astrocytes, and activated microglia. Notably, Aβ is not confined solely to the amyloid plaques but can also be detected in cortical arteries, CFS, plasma, and neuronal culture.[3,14] Amyloid plaques are classified by density and structure into diffuse plaques, with low fibril content,[15] and neuritic plaques, with high fibril content; the latter is considered a more significant indicator of AD.[3,16]

Advancements in AD Diagnosis: Criteria and Biomarkers:

Patients suspected of having AD should undergo multiple examinations, including neurological examination, neuronal magnetic resonance imaging (MRI), laboratory tests such as vitamin B12, and other tests, in addition to the patient's medical and family history.[1,17]

In 1984, The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) established clinical diagnostic criteria for Alzheimer's disease. The criteria consist of three categories: (1) Probable Alzheimer's disease, characterized by dementia confirmed through neuropsychological tests, progressive memory loss, impaired daily activities, and symptoms such as aphasia (speech disorder), apraxia (movement disorder), and agnosia (loss of perception), typically appearing between ages 40 and 90 in the absence of other systemic or brain diseases; (2) Possible Alzheimer's disease, applied when no other neurological or psychiatric disorders are present, although another illness (e.g., systemic or brain disorder) may exist but is not the primary cause of dementia; and (3) Definite Alzheimer's disease, confirmed through histopathological examination, such as a biopsy or autopsy.[1,18,19]

In 2011, the National Institute on Aging-Alzheimer's Disease Association updated the 1984 NINMCDS-ADRDA criteria with several modifications to improve the specificity and sensitivity of Alzheimer's disease diagnosis. In addition to clinical biomarkers, the newly proposed criteria include possible AD dementia with pathophysiological evidence for research purposes. There are two categories of Alzheimer's disease biomarkers: (a) markers of brain amyloid such as positron emission tomography (PET) and cerebrospinal fluid (CSF), and (b) markers of neuronal injury like cerebrospinal fluid tau, fluorodeoxyglucose (FDG) for metabolic activity, and magnetic resonance imaging (MRI) for atrophy measurement.[1, 20-22]

Although a definitive diagnosis of AD can only be made postmortem, the National Institute on Aging and Alzheimer's Association (NIA-AA) 2018 published a gold standard for *in vivo* diagnosis of AD in research. These include the AT(N) biomarker grouping, which encompasses amyloid (A) and tau (T) pathology, identified either through CSF assay or PET, and neuronal injury (N) evidenced by MRI, PET, or CSF.[9]

Exploring Retinal Biomarkers for Brain Amyloid Beta in AD:

The accumulation of Aβ in the brain is a hallmark feature of AD.[6,23,24] Advances in positron emission tomography (PET) imaging using Aβ-selective tracers have been extremely useful in confirming the clinical diagnosis of this disease. Still, the application of this method has been limited by its cost and accessibility. Therefore, PET imaging is currently not scalable for population screening of individuals at risk for AD.[6]

The brain is a hidden central nervous system (CNS) structure protected from external damage and can only be observed in its outer shell with one exception: the retina. Since the retina and forebrain share the same embryonic origin, they share anatomical and functional similarities and common disease manifestations.[25] The neural retina is a developmental product of the embryonic brain. It contains several molecular and cellular features common to the brain, including neurons, glial cells, interconnected blood vessels, and a protective blood barrier.[26-30] These features suggest that changes in the retina may correspond to changes in the brain, making them potential surrogate markers for CNS pathology.

In contrast to the brain, which is largely inaccessible for direct imaging, the retina can be easily imaged *in vivo* using optical imaging techniques such as fundus photography (FP), optical coherence tomography (OCT) and OCT angiography (OCT-A), Fluorescence lifetime imaging ophthalmoscopy (FLIO) and hyperspectral imaging (HIS).[9] These methods allow for non-invasive examination of the retina. Hyperspectral imaging measures the intensity of light reflected by tissue at multiple wavelengths, providing detailed spectral information with better resolution in a shorter processing time. Given that Aβ has a wavelength-dependent effect on light scattering, Xavier Hadoux *et al.* (2019) investigated the potential for *in vivo* retinal hyperspectral imaging as a biomarker of brain Aβ status. There were significant differences in retinal reflectance spectra on PET brain imaging between subjects with high Aβ burden and mild cognitive impairment (n=15) and age-matched PET negative controls (n=20). Retinal imaging findings correlate with brain Aβ load. The results will be verified using a second hyperspectral camera in an independent

cohort. Similar spectral differences were seen between control and 5xFAD transgenic mice, which accumulated Aβ in the brain and retina. These results indicate that retinal hyperspectral imaging can predict brain Aβ load.[6]

Recent Developments in AD Treatments: Disease-Modifying Treatments:

Six drugs are approved for the treatment of AD, including four cholinesterase inhibitors, an N-methyl-D-aspartate (NMDA) receptor antagonist (Memantine), and an anti-amyloid protein-like antibody (Aducanumab).[30] Current treatment options for AD are limited to drugs that provide mild symptom improvement. However, they do not change the underlying course of the disease.

Disease-modifying treatments or therapies (DMT) can alter the progression of AD and influence multiple pathophysiological mechanisms. DMTs, whether immunotherapies or small molecule therapies, are administered orally and are currently being developed to prevent AD or slow its progression.[1] These include gamma-secretase inhibitors/modulators (e.g., tarenflurbil and semagacestat) and beta-site amyloid precursor protein cleaving enzyme (BACE) inhibitors (e.g., verubecestat, atabecestat, and lanabecestat). Some BACE inhibitors have been shown to worsen cognitive performance in studies of adverse events such as hepatotoxicity. Monoclonal antibodies can be directed against monomeric, oligomeric, or plaque amyloid proteins. Several anti-amyloid monoclonal antibodies are currently in clinical trials.

Aducanumab attacks oligomer and plaque amyloid. It is the first approved disease-modifying therapy for AD (June 7, 2021). Although phase 3 EMERGE and ENGAGE trials were halted after efficacy and futility analysis suggested no benefit, additional data showed that the EMERGE trial had met the primary outcome on the Clinical Dementia Rating-Sum of Box (CDR-SB) score with marked plaque lowering.[30-32] The Food and Drug Administration (FDA) allowed its accelerated approval based on preliminary evidence that plaque lowering may predict clinical benefit. The FDA required a confirmatory phase 4 trial to produce additional evidence of aducanumab's clinical benefit. The accelerated approval of monoclonal antibodies has profound implications for AD drug development. It is based on biomarkers that predict clinical benefits. Aducanumab was approved for its ability to reduce plaque amyloid on amyloid PET. Other monoclonal antibodies such as donanemab, lacanemab, and gantenerumab are currently in clinical trials for AD.[31]

In the phase 3 study of lecanemab, the change from baseline in CDR-SB score (the primary endpoint) was less for lecanemab than for placebo at 18 months, which favored lecanemab. Results for secondary clinical endpoints were identical to those for the primary endpoint. Lecanemab exhibits high selectivity for soluble aggregated Aβ species and moderate selectivity for fibrillar amyloid compared with monomeric amyloid; this spectrum is thought to target the most toxic pathological amyloid species.[31,33-37] After 18 months of treatment in the amyloid substudy, the mean amyloid level of 22.99 centiloids in the lecanemab group was below the amyloid positivity threshold of approximately 30 centiloids, above which participants are considered to have elevated Brain amyloid levels. In cerebrospinal fluid substudy and overall population plasma analyses, reductions in markers of amyloid, tau, neurodegeneration, and neuroinflammation (plasma glial fibrillary acidic protein) were greater in the lecanemab group compared with placebo, except for NFL, which is less sensitive than other markers of neurodegeneration and has a slower time course of change than other markers.[38]

■ Conclusion

This review encompasses recent literature on AD diagnosis and treatment, with a specific focus on the role of Aβ. Limitations include the complexity of AD pathogenesis and the evolving nature of diagnostic criteria and therapeutic approaches. Although this article aims to provide a comprehensive overview, it may not capture all recent developments in the field.

AD presents a multifaceted etiology, with factors such as genetic predisposition, environmental exposures, and lifestyle factors contributing to disease development. The amyloid hypothesis emphasizes the role of Aβ aggregation in forming amyloid plaques, the classic pathological feature of AD. Understanding the molecular mechanisms of Aβ aggregation is critical for developing targeted diagnostic and therapeutic strategies. Although the landmark Alzheimer's paper by Sylvain Lesné *et al.* (2006) had to be retracted recently due to the usage of manipulated images, the Aβ hypothesis has been supported by many independent studies and is still considered a compelling approach to AD.[39]

Recent advances in AD diagnosis include the incorporation of clinical biomarkers, such as brain amyloid markers, into diagnostic criteria. Retinal hyperspectral imaging holds promise as a non-invasive biomarker of brain Aβ status and offers potential advantages over existing imaging modalities. Aducanumab, the first FDA-approved disease-modifying therapy for AD, targets Aβ pathology and represents a significant advancement in AD treatment. Other monoclonal antibodies targeting Aβ, such as Donanemab, Lacanemab, and Gantenerumab, show promise in ongoing clinical trials.

Retinal hyperspectral imaging offers a promising avenue for predicting brain Aβ burden. This non-invasive, cost-effective method may be used for population screening of individuals at risk of AD instead of PET, which is cheaper and more accessible.

While current therapeutic options for AD primarily target symptomatic relief, ongoing research into disease-modifying treatments (DMTs), either immunotherapies or small molecules, is being developed to prevent AD or decrease its progression.[1] Aducanumab is the first DMT for AD approved by the FDA (June 7, 2021), targeting oligomeric and plaque amyloid proteins. The approval was based on its ability to reduce plaque amyloid in amyloid PET.

Other monoclonal antibodies, such as donatumumab, lacanezumab, and gantenumab, are currently in clinical trials for AD. Lecanemab exhibits high selectivity for soluble aggregated Aβ species and moderate selectivity for fibrillar amyloid

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compared with monomeric amyloid; this spectrum is thought to target the most toxic pathological amyloid species.[31,33,34,36,37]

Advances in the research of Aβ as an AD biomarker offer great promise for improving the prognosis and quality of life of patients with Alzheimer's disease (AD). Hyperspectral imaging as a means of monitoring amyloid (Aβ) accumulation, coupled with developing disease-modifying therapies (DMTs) targeted explicitly at modulating Aβ pathology to alter disease progression, can potentially mitigate the associated severe consequences, including social and economic impacts.

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