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Review Article

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Revolutionizing Alzheimer's Diagnosis and Management: The Dawn of Biomarker-Based Precision Medicine

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ABSTRACT

Alzheimer's disease (AD), a leading cause of dementia, presents a formidable global health challenge intensified by the aging population. This review encapsulates the evolving landscape of AD diagnosis and treatment with a special focus on the innovative role of fluid biomarkers. Pathologically, AD is marked by amyloid beta (Aβ) plaques and neurofibrillary tangles of hyperphosphorylated tau, which lead to synaptic dysfunction, neuronal loss, and cognitive decline. These pathological changes, commencing decades before symptom onset, underscore the need for early detection and intervention. Diagnosis traditionally relies on clinical assessment, neuropsychological testing, and neuroimaging techniques. However, fluid biomarkers in cerebrospinal fluid and blood, such as various forms of Aβ, total tau, phosphorylated tau, and neurofilament light chain, are emerging as less invasive, cost-effective diagnostic tools. These biomarkers are pivotal for early diagnosis, differential diagnosis, disease progression monitoring, and treatment response evaluation. The treatment landscape is shifting toward personalized medicine, highlighted by advancements in Aβ immunotherapies, such as lecanemab and donanemab. Demonstrating efficacy in phase III clinical trials, these therapies hold promise as tailored treatment strategies based on individual biomarker profiles. The integration of fluid biomarkers into clinical practice represents a significant advance in AD management, providing the potential for early and precise diagnosis, coupled with personalized therapeutic approaches. This heralds a new era in combating this debilitating disease.

Keywords: Alzheimer's Disease; Amyloid Beta; Fluid Biomarker; Neurofilament Light Chain; Phosphorylated Tau

INTRODUCTION

Alzheimer's disease (AD) is a formidable challenge in global health, and is primarily driven by the rapid aging of the world's population. It is the most common cause of dementia, accounting for an estimated 60%–80% of all dementia cases,[1] and its impact is both profound and escalating. The total number of people suffering from dementia, which was at approximately 57.4 million as of 2019, is projected to skyrocket to an astounding 152.8 million by 2050.[2] This exponential increase underscores both a looming public health crisis, and a

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Conflict of Interest

The authors have no potential conflicts of interest.

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significant socioeconomic burden, with the global cost of dementia soaring from USD $(818 billion to an anticipated 2 trillion) from 2015 to 2030.[3] These figures paint a stark picture of a disease that is rapidly growing in prevalence and cost, posing a dire need for effective management and intervention strategies.

South Korea mirrors this global trend, with the country grappling with its own burgeoning AD crisis, particularly among its older population. Recent data have revealed that three-quarters of dementia cases in individuals over 65 years old are attributed to AD.[4,5] The number of older dementia patients, which stood at 794,280 in 2019, is expected to surge to 3,023,404 by 2050.[4,5] With the nation on the brink of entering a super-aged society in 2025,[5] the anticipated rise in dementia cases to over 1 million positions AD as a predominant health concern. This alarming trend has prompted the Korean Government and the Ministry of Health and Welfare to prioritize the prevention and treatment of AD, acknowledging its growing impact on the healthcare system and the nation's overall well-being.

From a pathological standpoint, AD is intricately complex.[6,7] It is characterized by the extracellular accumulation of amyloid beta (Aβ)-containing plaques and the ensuing Aβ-induced neuroinflammation (**Figs. 1A, C, 2A, and B**).[8] Compounding this is the development of intracellular neurofibrillary tangles, which are primarily composed of hyperphosphorylated tau protein (**Fig. 1A**). These pathological hallmarks of AD lead to progressive synaptic dysfunction and eventual neuronal loss (**Figs. 1B** and **2D**), culminating in cognitive decline and memory impairment synonymous with the disease (**Fig. 2E**). Understanding these pathological mechanisms is crucial for developing effective diagnostic and therapeutic interventions.

As the prevalence of AD continues to rise globally, the impact of the disease extends beyond the individual, straining healthcare systems and economies. Therefore, it is necessary to

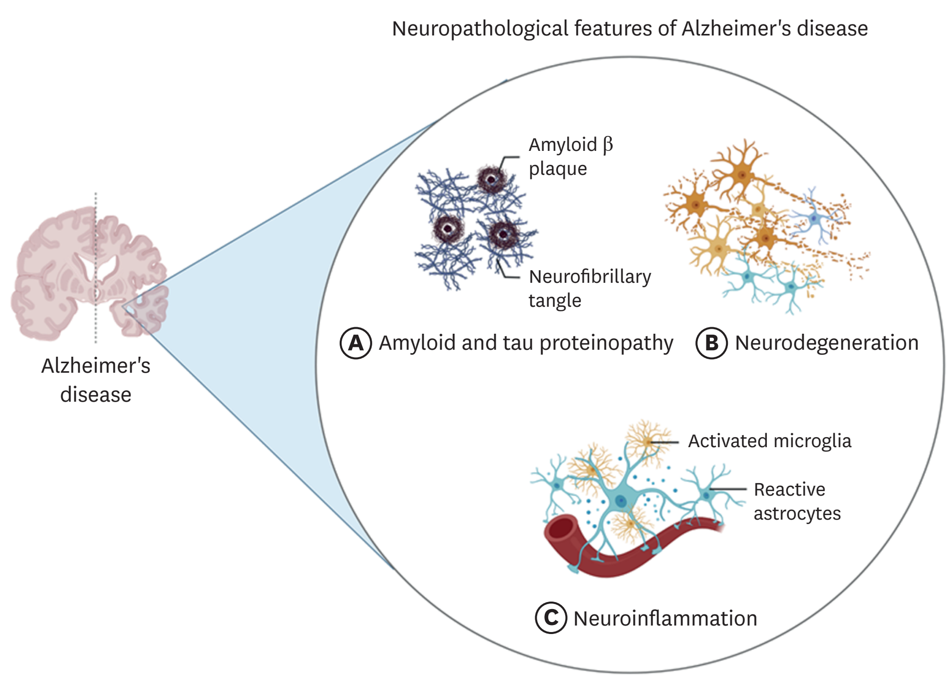

Fig. 1. Neuropathological features of Alzheimer's disease.

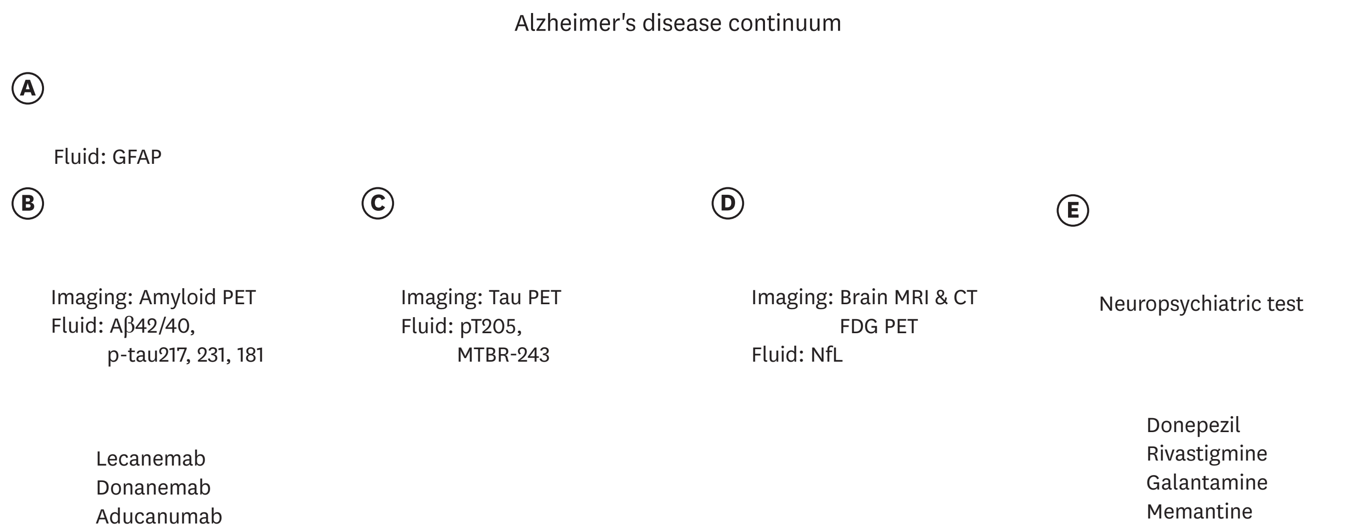

Fig. 2. Schematics of the AD continuum. (A) Amyloid proteinopathy is the initial neuropathological change of AD, which can be detected by amyloid PET or fluid biomarkers including Aβ42/40 and p-tau. (B) Anti-amyloid drugs, aducanumab, lecanemab, and donanemab, target amyloid. (C) The next stage is tau proteinopathy, which can be detected by tau PET or fluid biomarkers, including pT205 and MTBR-243. (D) Neurodegeneration can be monitored by anatomical brain MRI, FDG PET, or fluid biomarker NfL. (E) Finally, clinical symptoms appear. Medications including donepezil, rivastigmine, galantamine, and memantine, are targeting patients in this stage. Neuroinflammation, which can be monitored by GFAP, affects the progression of AD in diverse stages.
GFAP: glial fibrillary acidic protein, p-tau: phosphorylated-tau, PET: positron emission tomography, MTBR: microtubule-binding region, MRI: magnetic resonance imaging, CT: computed tomography, FDG: fluorodeoxyglucose, NfL: neurofilament light chain, AD: Alzheimer's disease.

urgently adopt advanced diagnostic techniques, effective treatments, and comprehensive management strategies.

This review shows the current state of AD by examining its epidemiology, pathology, and the strides being made in its diagnosis and treatment, particularly in the context of fluid biomarkers. By exploring these facets, we hope to shed light on potential pathways to mitigate the burgeoning impact of AD in an increasingly aging world.

PATHOLOGICAL PROGRESSION OF AD

AD initiates diverse pathological change in the human brain prior to the manifestation of clinical symptoms (**Fig. 2**). The earliest pathological change associated with AD is the deposition of Aβ peptides (**Fig. 2B**), which can start as early as two decades prior to the onset of mild cognitive impairment (MCI).[9,10] This early accumulation of Aβ is critical, as it sets the stage for the subsequent cascade of neuropathological events.[9]

As the disease progresses, tau proteins, another key biomarker of AD, undergo abnormal changes, resulting in hyperphosphorylation.[9,10] This leads to the formation of neurofibrillary tangles inside neurons, disrupting their normal function, and causing neuronal injury.[10] The interplay between the accumulating Aβ plaques in the brain and the formation of tau tangles is a hallmark of AD's progression. In particular, these tauopathies are closely associated with the cognitive decline characteristic of AD, indicating a direct correlation between the extent of tau pathology and the severity of cognitive impairment.[11]

clinical settings for the early detection of AD. Further stratification of participants based on their dementia status shows that this combination of biomarkers demonstrated better AUC values, particularly in participants with dementia. Such data underscore the efficacy of these biomarkers, not only in detecting amyloid pathology, but also in distinguishing between various stages of cognitive impairment.

The subsequent phase of the study aimed to assess the ability of blood biomarkers to predict cognitive-stage transitions. For this purpose, we measured plasma p-tau181, cortical thickness, hippocampal volume, amyloid positivity, cognitive function, and demographic factors in the KBASE-V cohort. Our results indicated that a combination of plasma p-tau-181, centiloid value from amyloid PET, age, and semantic fluency presented a high predictive ability for cognitive stage transitions within a 3-year timeframe, with considerably high probabilities.[41] When focusing on participants with MCI, the predictive accuracy, as denoted by the AUC, was remarkably higher. This finding suggests that with these biomarkers, it is possible to predict MCI progression with a high degree of certainty.

GFAP has recently emerged as a notable biomarker in Alzheimer's research. A study published in Nature Medicine this year highlighted the critical role of astrocytes in the progression of AD pathology, particularly in the preclinical stages.[42] The study posited that detecting abnormalities in astrocyte reactivity biomarkers in the blood is essential to predict the development of tau pathology and subsequent clinical symptoms in individuals who are cognitively unimpaired, yet Aβ positive.[42]

Initially, it was hypothesized that the NfL could be a specific biomarker for AD.[43] However, this notion has evolved; while NfL is no longer considered AD–specific, consensus has been reached on its value as a fluid biomarker to evaluate neurodegeneration.[44] Current methodologies do not permit the diagnosis of neurodegenerative diseases based solely on serum NfL levels; nevertheless, their potential to assess the extent of neurodegeneration, and possibly the therapeutic effects of treatments, is significant. Notably, in our previous study,[45] serum NfL level demonstrated a strong correlation with brain atrophy, particularly in regions such as the hippocampus and medial temporal lobe.

Soluble triggering receptor expressed on myeloid cells 2 (sTREM2) was a focal point of interest following genome-wide association studies that identified a TREM2 mutation as a significant genetic factor in AD.[46,47] In our research involving the Asan cohort, we measured plasma soluble TREM2. Our findings indicated that plasma sTREM2 was not specific to AD, but rather showed a high correlation with age.[31] We now understand that plasma sTREM2 originates from peripheral macrophages, reducing its specificity as a biomarker for AD.[48]

In another segment of our study, we compared several fluid biomarkers in the CSF and plasma, and found that while some biomarkers showed high correlations between the CSF and plasma, others did not.[31] This underscores the need for careful consideration when employing blood biomarkers for the diagnosis and follow-up of AD, as certain plasma biomarkers may not correlate well with their CSF counterparts.

In summary, various fluid biomarkers detectable in both CSF and plasma have been consistently linked to alterations in Aβ levels, beginning approximately 20 years before symptom onset. Subsequent changes in p-tau217 and p-tau181 follow a well-established sequence,[49] enabling the potential diagnosis of AD based on fluid tests.

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TRANSFORMING AD MANAGEMENT: THE INTEGRAL ROLE OF FLUID BIOMARKERS IN CLINICAL TRIALS AND DIAGNOSIS

Recognizing the burgeoning role of blood biomarkers in AD research, the Clinical Trials on Alzheimer's Disease (CTAD) task force conducted an exhaustive review of several clinical trials that incorporated these biomarkers.[50] Their comprehensive analysis, published June 13, 2023, provides critical insights into the evolving landscape of AD diagnosis and management. The taskforce's findings underscore the increasingly prevalent use of various blood biomarkers in the prescreening stages of recent phase 2 and 3 clinical trials.[50] This strategy has been instrumental in refining the selection process for participants, particularly focusing on individuals who exhibit heightened suspicion for AD based on initial biomarker assessments.

One notable example is the ongoing TRAILBLAZER-ALZ3 clinical trial (https://classic.clinicaltrials.gov/ct2/show/NCT05026866), which exclusively utilizes plasma p–tau217 as a screening tool.[50] The decision to rely on p-tau217 reflects a growing confidence in the specificity and sensitivity of this particular biomarker in identifying individuals at various stages of AD. This targeted prescreening approach helps streamline the clinical trial process, enabling a more efficient and accurate identification of suitable candidates for further investigation.

The advancing understanding and application of fluid biomarkers have also influenced ongoing revisions of the diagnostic criteria for AD, specifically within the context of the 2024 revised criteria and staging of AD.[25] The general consensus is that the integration of fluid biomarkers into diagnostic criteria represents a considerable step forward, and current suggestions that heavily incorporate the use of fluid biomarkers are unlikely to undergo substantial changes. This underscores the need for the medical community to familiarize itself with the nuances and applications of fluid biomarkers in AD diagnosis and management.

In clinical trials, fluid biomarkers for AD fulfill critical functions, including prescreening, screening, and patient monitoring.[51] Their utility extends beyond the research setting to clinical practice, where these biomarkers offer substantial advantages. For example, in the prescreening of patients with AD, fluid biomarkers are a cost-effective and less invasive alternative to amyloid PET imaging. This approach is particularly advantageous, given the high costs and limited accessibility associated with PET imaging.

Moreover, fluid biomarkers are invaluable in the context of prescribing new and often expensive pharmacological interventions, such as lecanemab and donanemab.[14,15] These drugs, which represent the cutting edge of AD therapy, require precise patient selection to ensure both efficacy and cost-effectiveness. Biomarkers aid in this selection process by providing objective and quantifiable data that can inform clinical decision-making.

Fluid biomarkers are instrumental in the early evaluation of therapeutic efficacy. Upon initiating new treatments, it is imperative to monitor their impact accurately and efficiently. Fluid biomarkers offer a means of tracking disease progression and treatment response in real-time, providing clinicians with vital information to adjust therapeutic strategies as needed.

In conclusion, the integration of fluid biomarkers into the diagnostic and therapeutic landscape of AD represents a pivotal advancement in the approach to this complex and

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challenging condition. As research continues, the potential of these biomarkers to transform the diagnosis, management, and treatment of AD becomes increasingly apparent. The medical community must therefore remain abreast of these developments, integrating fluid biomarkers into clinical practice to enhance patient care and treatment outcomes in AD.

CONCLUSION

It is pertinent to underscore that the field of AD diagnosis and treatment is undergoing a transformative shift, propelled by the advances in precision medicine. Historically, the diagnosis of AD has been predominantly based on clinical observations and symptomatology. However, with the emergence and refinement of imaging technologies such as MRI and PET, a substantial leap toward more accurate and precise diagnostic methodologies has been made.

The future trajectory of AD management is expected to be significantly influenced by the incorporation of various fluid biomarkers into clinical practice. These biomarkers can revolutionize the process of diagnosing and monitoring AD, facilitating the implementation of more personalized and targeted therapeutic interventions. Accurate and early diagnosis made possible by these advances allows the application of a spectrum of treatment modalities that are specifically tailored to the individual patient's stage and characteristics of the disease.

For example, in patients with MCI or early-stage dementia attributable to AD, interventions may include the modulation of modifiable risk factors and administration of Aβ immunotherapies. These strategies aim to intercept and mitigate disease progression at an early stage. In contrast, for patients with more advanced stages of dementia due to AD, therapeutic approaches may align more closely with the current standards of care, focusing on symptom management and enhancing the quality of life.

Regarding the horizon of AD treatment, emerging therapies, such as gene therapy and the use of nanoparticles, are potential groundbreaking modalities. These novel approaches are indicative of the ongoing evolution in the field, reflecting a shift toward more innovative and potentially more effective strategies to combat the complexities of AD.

The landscape of AD diagnosis and treatment is evolving rapidly, driven by technological and scientific advances. The integration of these new tools and methods promises to bring about a more nuanced understanding of the disease, and open new avenues for the effective management and treatment of AD.

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