The Biochemistry Behind Cognitive Decline: Biomarkers of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most prevalent type of dementia. Pathologically, the disease is marked by neurofibrillary tangles (NFT), which are aberrant accumulations of the tau protein that develop inside neurons, and extracellular plaque deposits of the amyloid β peptide (Aβ). These pathological lesions are present in the brain before the beginning of clinical manifestations. However, despite advancements in the comprehension of AD pathophysiology, timely and accurate clinical diagnosis remains challenging. Therefore, developing biomarkers capable of detecting AD during the preclinical phase holds enormous promise for precise diagnosis since detecting the disease early is crucial because it enables interventions when treatments may be more effective. This article intends to provide a comprehensive review of AD biomarkers, discussing their significance, classification, and recent developments in the field.

Abbreviations:
NFT: neurofibrillary tangles, APP: amyloid precursor protein, PSEN1: presenilin1, PSEN2: presenilin2, SPECT: single photon emission computed tomography, CT: computed tomography, FDG-PET: 18F-fluorodeoxyglucose-positron emission tomography, MRI: magnetic resonance imaging, CSF: cerebrospinal fluid, BBAD: blood biomarkers in AD

Introduction:

Alzheimer's disease (AD) was discovered more than a century ago. It is the most common neurodegenerative disorder in older adults, which results in loss of memory, language, visuospatial abilities, and other mental functions (1). Worldwide, the case rate of AD doubles every five years after age 65. In addition, it is expected that there will be 115 million cases by 2050 (2). People suffering from the disease's latter stages are bedridden and need care 24 hours daily. AD is eventually fatal. According to researchers, early AD diagnosis will be crucial to halting, slowing, or delaying the illness. Therefore, much attention is being put on understanding AD's pathophysiology and establishing early diagnosis and efficient intervention due to the disease's severe economic and societal costs.

Pathophysiologically, AD is characterized by extracellular deposits of the protein beta-amyloid (also known as beta-amyloid plaques) and the buildup of a particular type of protein tau (also known as tau tangles) inside neurons. These changes lead to the destruction of neurons that cause memory loss and other symptoms of AD (3). Physicians typically rely on clinical symptoms for diagnosing AD. However, neuronal loss and neuropathologic lesions are already evident in many brain regions when AD is clinically diagnosed (3). A key objective of biomedical research is identifying preclinical markers of AD (i.e., biomarkers) that permit early diagnosis and intervention. These biomarkers enable clinicians to recognize individuals at risk before observable cognitive decline, thereby allowing for potentially more effective early interventions to preserve cognitive function. This article aims to provide a concise and current overview of AD biomarkers, focusing on their importance in early detection, diagnosis, and treatment monitoring and discussing the challenges associated with their application.

Understanding AD:

Risk factors:

AD, a complex neurodegenerative condition, has been related to a number of risk factors. While age remains the most critical risk factor, research has shown many other characteristics contributing to an individual's susceptibility to the disease. The major other unmodifiable risk factor is genetic, with one APOE ε4 allele raising the risk of developing AD threefold, and two APOE ε4 alleles increasing the risk up to twelvefold. Modifiable risk factors for AD include hypertension, diabetes, hypercholesterolemia, smoking, alcohol consumption, obesity, and diet. On the other hand, physical activity, education, entertainment, and social interaction have all been proven protective factors (4). Table 1 summarizes some of the major risk factors for AD.

Table 1: AD risk factors

Risk factor	**Description**
Age	The main risk factor for AD is advancing age, with 10–30% prevalence in the population older than 65, with an incidence at least doubling every ten years after age 60 (5).
Sex	Women are more likely to develop AD.
Genetics	- Family history of AD - The existence of the APOE ε4 allele - Trisomy 21 and family history are risk factors for early-onset dementia.
Lifestyle Factors	Cardiovascular health, which involves hypertension and elevated cholesterol, smoking, obesity, diabetes, dietary habits, physical inactivity, and lack of intellectual and social activity (6).
Environmental Factors	Exposure to toxins or certain chemicals and traumatic brain injuries.
Mental Health	Conditions like depression and chronic stress increase the risk of AD.
Sleep Disorders	Sleep disturbances may contribute to cognitive decline.

Abbreviations: AD: Alzheimer's disease; APOE ε4: apolipoprotein E-ε4;

Pathophysiology:
AD is marked by brain shrinkage and abnormal deposits called plaques and neurofibrillary tangles (NFT). Plaques are microscopic lesions characterized by a spherical shape, consisting of an extracellular core composed of amyloid beta (Aβ) peptide. At the same time, NFT are intracytoplasmic structures and consist of twisted coupled spiral fibrillary proteins known as tau, found within neurons. The amyloid precursor protein (APP) is a membrane protein that is found mostly in synapses. In standard non-amyloidogenic processing, APP undergoes cleavage by α-secretase, followed by γ-secretase. Subsequently, the resulting fragments are processed and removed correctly. In individuals diagnosed with AD, the amyloidogenic processing pathway involves the sequential action of β-secretase and γ-secretase on APP, resulting in the generation of amyloid-β (Aβ) fragments, with a specific emphasis on Aβ1-42. Extracellular plaques arise as a result of the increased accumulation in conjunction with reduced clearance processes. Aβ deposits form around meningeal and cerebral blood vessels, as well as gray matter. Tau is a protein that stabilizes the microtubule in neuronal axons in a healthy state. Due to the extracellular Aβ aggregation in AD, tau is hyperphosphorylated, which leads to tau aggregates and polymerization into fibrillar structures that destabilize microtubules and produce NFT, which are found within both glial and neuronal cell types in the affected cortical and subcortical brain regions. The presence of these pathogenic proteins and free radicals leads to the activation of microglia, neuroinflammation, damage to mitochondria, oxidative stress, deficits in neurotransmitters (specifically acetylcholine), malfunction in synaptic activity, and finally, the loss of synapses and neurons, which leads to memory loss and cognitive deterioration(5–8).

Challenges in Clinical Diagnosis:
While our understanding of AD biology has evolved significantly, diagnosing the disease remains challenging. The medical diagnosis of AD relies on conducting neuropsychological assessments, which typically involve evaluating memory loss and cognitive decline and carefully excluding other dementias commonly occurring with advancing age, among them cerebrovascular disease, dementia with Lewy bodies, cerebral tumor, normal pressure hydrocephalus, frontotemporal lobar degeneration, or depression (9,10). The clinical identification of AD exhibits limited reliability, particularly in the initial phases of the disease. Based on autopsy validation, the clinical diagnosis of AD compared to non-AD conditions demonstrates an overall accuracy rate of 78% (11). Misdiagnosis of AD is especially common in its initial phases when signs are subtle or mild, and in primary care, in which over half of patients having cognitive impairment are not detected or appropriately diagnosed (12). This misinterpretation leads to inadequate care and treatment, retarded or erroneous interventions, and incorrect data regarding condition and outcome (13). Neuropathological alterations occur years before clinical manifestations of AD. Pathological NFT composed of phosphorylated tau protein accumulate in brain cells during the presymptomatic stages of AD. In addition, distinct isoforms of amyloid-β (Aβ) peptide deposits accumulate in the extracellular space. These proteins are secreted into the CSF, where they are detectable (14). Efforts have been undertaken in recent years to develop reliable biomarkers and sophisticated imaging techniques to aid in early and accurate AD diagnosis, thereby addressing a significant need in clinical practice.

AD biomarkers:
Biomarkers: Definition and Types:
A biomarker is a measurable characteristic that signals healthy physiological functions, pathologic biological events or biological reactions to an exposure or intervention, which include therapeutic responses. Biomarkers can consist of molecular, histologic, radiographic, or physiological traits. Biomarkers fall into the following categories: susceptibility/risk, diagnostic, monitoring, prognostic, and predictive biomarkers (15). The perfect AD biomarker should meet several requirements, including 1) being able to identify AD with high specificity and sensitivity; 2) the aptitude to recognize the earliest stages and monitor the evolution of AD; 3) usefulness for assessing medical effectiveness; and 4) the need for specimens which could be collected quickly, numerous times, in a noninvasive manner, and affordably (16). Biomarkers for AD include genetic markers (17), neuroimaging markers such as PET scans and MRI (18), and biochemical markers such as amyloid beta and tau proteins (19).

Genetic Biomarkers:
The genes AβPP, PSEN1, and PSEN2 have been significantly associated with the development of early-onset AD, which often manifests before age 65 and is exceptional (5% of AD cases). On the other hand, late-onset AD (the most prevalent form) has primarily been linked to the apolipoprotein E-ε4 (APOE ε4) gene, which is suggested to elevate AD risk essentially by modulating Aβ accumulation (20,21). Genetic AD biomarkers (mutations in AβPP, PSEN1, and PSEN2) are just helpful in detecting familial AD (more than 95% of AD cases are isolated and lack mutations in these three genes). On the other hand, the APOE ε4 mutation is a known risk factor for late-onset AD, but it is not a reliable genetic biomarker for diagnosis. Because of lower prices and faster analysis, testing for AD-associated genes using focused sequencing methods such as Sanger or next-generation sequencing became increasingly popular compared to complete-exome sequencing over time. Nevertheless, genetic testing for AD is not usually recommended. It is sometimes used in families with rare early-onset forms of AD (6).

Neuroimaging-based Biomarkers in AD:
Human in vivo neuroimaging provides a deeper comprehension of the pathophysiology of AD. These examinations are essential for identifying non-AD etiologies contributing to cognitive loss (e.g., strokes or cerebral tumors) and providing diagnostic support for AD (22). MRI and CT allow visualization of gray matter, white matter, and CSF. They help characterize supportive features for diagnosing AD, especially brain atrophy. They also permit the elimination of non-AD causes of cognitive decline (22). The PET scan is another neuroimaging technique commonly used in AD research and diagnosis. It works with radiolabeled tracers specific to Aβ, such as Flutemetamol, Pittsburg compound B, and F-florbetapir (23,24). Other Functional neuroimaging techniques for identifying dysfunctional brain regions include functional MRI (fMRI), which examines blood flow in the brain, and SPECT, which investigates brain perfusion as a measure of brain metabolism. Despite their contributions to our comprehension of AD, these neuroimaging techniques have limitations that must be considered—specifically, the requirement for costly equipment and specialized training.

CSF Biomarkers in AD:
Because the brain's extracellular space is in intimate contact with the CSF, modifications in the physiology of nervous system may be detected in the CSF. The two most well-known neuropathologic signs of AD are Aβ deposits and tau protein NFT. CSF biomarkers that have been established reflect the pathophysiology of these two features. When comparing AD patients to normal controls, Aβ1-42 concentrations in CSF are lower, although total tau (T-tau) and phosphorylated tau (P-tau) concentrations are higher. This decline in Aβ1-42 in the CSF of Alzheimer's patients occurs because Aβ accumulates into plaques, trapping the peptide in cerebral tissue, resulting in a decreased capacity for Aβ to diffuse into the CSF (25). Tau found in CSF may be associated with the passive discharge of intracellular content from dead cells. Still, multiple studies show that tau secretion also involves active cellular processes (26). In contrast to Aβ, NFT appear later in the progression of AD (27). Moreover, high CSF tau has been linked with rapid transformation from mild cognitive impairement to AD, tissue injury, and the likelihood of poor clinical outcome (28–30). T-tau is not specific to AD but indicates brain degeneration or injury. It is elevated in the brains of various neurodegenerative disease patients (25). On the contrary, increased P-tau, which denotes hyperphosphorylated tau protein, is associated with NFT formation in the brain (31,32). Aβ1-42 and tau Protein can be measured using immunological techniques such as ELISA and electrochemiluminescence and non-immunological techniques such as mass spectrometry (MS). Multiple studies supported by evidence have shown that using the CSF Aβ1-42/1-40 ratio is more effective than the total amount of CSF Aβ1-42. This approach enhances the accuracy of diagnoses. Similarly, in terms of PET scan consistency, using CSF P-tau/Aβ1-42 or T-tau/Aβ1-42 ratios is more reliable compared to relying exclusively on T-tau or P-tau, respectively, or Aβ1-42 alone (33,34). However, the significant inter-laboratory variability in analyte concentrations can restrict the usefulness of CSF biomarker assays. Therefore, it is necessary to enhance assay development quality control specifications to assure minimal total calibration variation and strict variability limits between lots(19). For this reason, The Alzheimer's Association Quality Control program for CSF biomarkers, which includes 84 laboratories worldwide, and the Working Group for CSF proteins of the International Federation of Clinical Chemistry (IFCC) have initiated work to create uniform procedures and unify levels between assay techniques to tackle these problems and adjust results over laboratories (24). According to a recent meta-analysis (35), clinicians can use CSF biomarkers as a valuable supplementary diagnostic test when evaluating patients with cognitive disorders. Specifically, CSF biomarkers enhanced physicians' assurance of diagnosing AD and impacted patient management. It is advisable to include CSF AD biomarkers as a standard practice in assessing patients with mild cognitive impairment and dementia. They are suggested for accurate and timely diagnosis, differential diagnosis, and predicting the probability and progression of neurological deterioration (36). The kits and methods that are often used for measuring CSF Biomarkers of AD are included in Table 2.

Blood biomarkers in AD (BBAD):
Given the invasiveness and cost of CSF and neuroimaging biomarkers of AD, there is a pressing need to explore and develop reliable BBAD. Despite the common perception that AD is a brain disease, it has been shown that AD is a systemic condition which manifests in peripheral tissues beyond the central nervous system (CNS) throughout the earlier stages of the disease. Furthermore, biomolecules are continuously exchanged between the circulation and CSF (37). The latest innovations in BBAD for identification, prognosis, and monitoring therapy include plasma Aβ1-42/1-40 ratio, P-tau levels, serum neurofilament light chain, and glial fibrillary acidic protein (38). However, several difficulties must be addressed before BBAD may be considered a routine component of clinical therapy. Interference of circulating blood proteins and the reduction in the concentration of proteins and other analytes as they travel from the brain tissue to the CSF and into the circulation pose a significant quantitative identification challenge (39). Moreover, there are few available prospective studies in which plasma samples were collected continuously over an extended period, and clinical efficacy was calculated from a predetermined cut point. Before adopting a specific BBAD or any combination of BBAD in clinical practice, it is recommended that such data be gathered through clinical studies (38). The kits and methods that are often used for measuring BBAD are included in Table 3.

Table 2: Kits and methods that are often used for measuring CSF

Fluid	Biomarker	Commerical kits	Technique	Label	
				USA	EU
CSF	Aβ42	INNOTEST, Fujirebio	ELISA	RUO	CE Marked
		Lumipulse, Fujirebio	CLEIA	RUO	CE Marked
		Elecsys, Roche Diagnostics	ECLIA	BDD	CE Marked
		Euroimmun, PerkinElmer	ELISA	N/A	CE Marked
		TECAN, Ibl-international	ELISA	RUO	CE Marked
		ADMark, Athena Diagnostics	ELISA	LDT	N/A
	Aβ42/Aβ40 ratio	Lumipulse, Fujirebio	CLEIA	FDA approved	CE Marked
		Euroimmun, PerkinElmer	ELISA	N/A	CE Marked
		TECAN, Ibl-international	ELISA	RUO	CE Marked
		ABtest-IA, Araclon Biotech	ELISA	RUO	CE Marked
	P-tau-181	INNOTEST, Fujirebio	ELISA	RUO	CE Marked
		Lumipulse, Fujirebio	CLEIA	RUO	CE Marked
		Elecsys, Roche Diagnostics	ECLIA	BDD	CE Marked
		Euroimmun, PerkinElmer	ELISA	N/A	CE Marked
		TECAN, Ibl-international	ELISA	N/A	CE Marked
		ADMark, Athena Diagnostics	ELISA	LDT	N/A
	T-tau	Lumipulse, Fujirebio	CLEIA	RUO	CE Marked
		Elecsys, Roche Diagnostics	ECLIA	BDD	CE Marked
		Euroimmun, PerkinElmer	ELISA	N/A	CE Marked

Table 3: Kits and methods that are often used for measuring BBAD

Fluid	Biomarker	Commerical kits	Technique	Label	
				USA	EU
Plasma	Aβ42/ Aβ40 ratio	HISCL β-Amyloid, Sysmex	CLEIA	N/A	CE Marked
	P-tau-181	Simoa Advantage V2Kit, Quanterix	Single molecule array (SiMoA)	BDD	N/A
	Panels: Aβ42/ Aβ40 ratio, APOE ε4	PrecivityAD, C_2N Diagnostics	LC-MS/MS	BDD	CE Marked
	P-tau-181, APOE ε4	Elecsys Amyloid Plasma Panel, Roche Diagnostics	Elecsys immunoassays	BDD	N/A

Abbreviations: CSF: Cerebrospinal fluid; Aβ42: Amyloid β-protein 42 ; ELISA: enzyme-linked immunosorbent assay ; RUO : Research Use Only ; CE : *Conformité Européenne* ; CLEIA: Chemiluminescence enzyme immunoassay ; ECLIA: Electrochemiluminescence immunoassay ; BDD: Breakthrough Devices Program ; N/A: not available ; LDT: Laboratory Developed Test ; Aβ40: Amyloid β-protein 40 ; FDA: Food and Drug Administration ; APOE ε4: apolipoprotein E-ε4; LC-MS/MS: Liquid chromatography–tandem mass spectrometry

Future Directions in AD Biomarkers:

Many studies are being conducted in the area of AD biomarkers; prospects include the discovery of biomarkers that can evaluate each stage of disease pathogenesis and enable a precise diagnosis of the condition in its earliest stages. In addition, recent advances in developing proteomics, metabolomics, mass spectrometry, and using exosomes and investigating microRNA profiles revealed promising prospects for blood-based biomarkers as AD screening tools (40). Blood cell-derived biomarkers are an additional area of research with promising potential. Changes in peripheral cells such as platelets, lymphocytes, and erythrocytes have been observed in AD, rendering them potential biomarkers for studying neuronal pathology (41). Blood platelets, which share biochemical properties with neurons, can be used as a basis for comprehending the pathology of AD (42). Through the blood-brain barrier, lymphocytes, essential to neuroinflammatory processes, migrate from the circulation to the Alzheimer's brain. The combination of these neuroinflammatory elements in the blood and the alterations observed in the lymphocytes of patients with AD has the potential to serve as blood cell-based biomarkers for condition (43). The presence of molecules such as β-amyloid peptide, heat shock protein 90, band three protein, and calpain 1 in erythrocytes indicates their potential as preclinical biomarkers. Furthermore, red blood cell morphology is significantly altered in AD (44). However, despite these promising features, additional research is required to explore their diagnostic potential thoroughly (41).

Conclusion:

AD is a form of dementia characterized by irreversible progression and lengthy prodromal phases. Utilizing minimally invasive diagnostic tests that assess biomarkers might present the most effective option for diagnosing AD in its early stages instead of relying only on clinical evaluations. The use of biomarkers for AD diagnosis has gained popularity over the past two decades. However, their efficiency in early AD diagnosis and routine screening is questioned due to their employment of invasive procedures, high expense, and measurement uncertainty. PET scan and CSF markers are more often utilized diagnostic biomarkers in clinical studies; however, they have practical issues (e.g., expense and access). As sensitive and novel technical approaches are developed, and research design is given more significant thought, possibilities for biomarkers for AD will be carefully assessed.

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The researcher has no conflict of interest to declare.

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