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Application and challenges of biomarkers for the prognosis and diagnosis of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is an age-based neurological problem characterized by dementia.AD has become a serious concern for public health with an expected threefold increase in Alzheimer's cases by 2050. Various treatments are available for the treatment of AD. However, a big challenge is the late diagnosis of AD which can affect the treatment outcomes. Particularly in the aging brain, AD pathology can often co-occur with other neurodegenerative and vascular illnesses. For this reason, prompt differential diagnosis is essential to provide the right care, support, and customized treatment regimens. Diagnosis of AD at early stages (prognosis) when the changes are very mild can be beneficial. At present, several potential biomarkers are available for evaluation and diagnosis of AD. Biomarkers-based early detection of AD can enable scientists to find new treatments and approaches to prevent or delay dementia. Structural and functional imaging of the brain with the help of magnetic resonance imaging, and positron emission tomography scans are some widely used methods to screen AD. Analysis of body fluids such as blood, cerebrospinal fluid, saliva, and urine for AD-associated proteins to aid in the diagnosis of AD pathology. In this article, currently used biomarkers for AD are reviewed. A comparative overview of various biomarkers with their applications, advantages, and disadvantages is given in a table form. Recent developments in the field of AD diagnosis have been highlighted.

INTRODUCTION

Alzheimer's is a type of neurodegenerative disease that is characterized by progressive dementia [1,2]. Alzheimer's disease (AD) mainly affects elderly people, as 50%–70% of the elderly population suffers from it [3]. The global burden of this disease is growing very fast, and it is estimated that the number of AD patients will double every 20 years, reaching over 66 million in 2030 and 100 million by 2050 [4]. The disease normally has a gradual onset followed by ongoing cognitive loss. Memory loss, confusion, and impairments of cognitive function are some of the first noticeable signs of AD that seriously impair the social or occupational performance of the patients [5–12]. On average, it takes about 8.5 years for a person to die after their first appearance of clinical symptoms [13]. The early symptoms of AD in its preclinical stages include hyperphosphorylated tau (p-tau) aggregation in neurofibrillary tangles, amyloid beta (Aβ) accumulation in senile plaques, and ultimately cell death. The development of Aβ plaques, which are an underlying neuropathology feature of AD, is thought to occur 15–20 years before the clinical presentation of the illness and is followed by the build-up of improperly phosphorylated tau in neurofibrillary tangles [14]. Other metabolic systems, such as neurotransmitter metabolism, lipid synthesis, inflammation, and mitochondrial function, are all disturbed in AD. Amyloid plaques are extracellular hydrophobic deposits of the Aβ peptide and are frequently categorized as diffuse or dense core depending on their morphology and whether they stain positively for dense core or negatively for diffuse core with congo-red or Thioflavin-S, both of which are specific dyes for the conformation of the β-pleated sheet [15]. Dominant mutations in one of the three disease genes (PSEN1, PSEN2, or Amyloid precursor protein (APP)), which are all connected

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to the production of Aβ, account for 10%–15% of all AD cases. Still, the great majority of sporadic cases have an etiology that is not understood. APP is cleaved by the α-secretase enzyme into α–APP and C–83 in healthy conditions. Additionally, APP can be broken down by the enzymes β and α-secretases to produce the peptides Aβ40 and Aβ42. The Aβ42 species are more likely to assume a beta-sheet shape and can therefore aggregate more easily to oligomers, bigger prefibrillary species, and insoluble plaques. The prefibrillar species are thought to possess neurotoxic qualities. Additionally, the presence of plaques can activate microglia, which in turn triggers the release of excessive amounts of proinflammatory cytokines, promoting the production of Aβ42 by the neurons and causing oxidative damage. The construction and stability of microtubules, a crucial part of the neuronal cytoskeleton, are dependent on the microtubule-associated protein, which has six primary isoforms. Neurofibrillary tangles are made of abnormally p-tau build-up in the brains of AD patients. The accumulation of defective Aβ and tau is assumed to cause the severe loss of neurons or synapses and inflammatory processes in the AD brain [4].

BIOMARKERS OF AD

Biomarkers are crucial for improving therapy development and diagnostics in the medical field [16–19]. Eventually, the use of biomarkers in AD could aid in the prediction of disease progression from the asymptomatic stages to full-blown AD [4]. Positron emission tomography (PET), structural magnetic resonance imaging (MRI), cerebrospinal fluid (CSF), and fluoro-deoxy-d-glucose (FDG)-PET measurements of Aβ and tau are the most often employed biomarkers in clinical trials for dementia. However, structural changes detected by MRI are probably present at relatively advanced stages of the illness. PET imaging is somewhat expensive and has restricted availability. In addition, FDG-PET and structural MRI are indirect measurements of the primary pathology indicators of AD (Aβ and tau), which may make them less specific for AD in some circumstances. Biomarkers used in the prognosis and diagnosis of AD have been summarized in Table 1.

Neuroimaging or brain imaging

This technique is used to detect AD in the early stages of progression. [20]. Structural imaging, functional imaging, and molecular imaging are the methods of neuroimaging [21–24].

Structural imaging

This method used MRI and CT scans to detect AD. It gives information about the structure of the brain such as its shape, size, volume, and position of brain tissues. In patients with AD shrinkage of the hippocampus can be seen as an early sign of Alzheimer's.

Functional imaging

FDG-PET scans are used to check the changes in functions of the brain due to AD. The changes in blood circulation and cell metabolism are detected in this method. A person suffering from AD has a decrease in brain cell activity in some regions. In AD, FDG-PET imaging indicates a decrease in the consumption of glucose by the brain that is required for memory and problem solving

Molecular imaging

This method also uses PET scans to diagnose AD in its early stages to prevent its effect on memory, reasoning, learning, and thinking. FDA-approved four radiopharmaceutical medicinal products used in molecular imaging techniques. These agents are Neuraceq® injection containing Florabetaben, Amyvid® injection containing florbetapir, and Vizamyl® containing flutemetamol used with PET scan to detect beta-amyloid in the brain. Elli Lilly and company got FDA approval for Amyvid® [25] in 2012 as a diagnostic agent. Neuraceq® by Piramal Imaging got FDA approval on 19 March 2014 for PET imaging in the diagnosis of AD [26]. GE Healthcare received FDA approval [27] for Vizamyl® in October 2013 to detect amyloid neuritic plaque density for AD. Eli Lilly and company got FDA approval in 20020 to use Tauvid® containing Flortaucipir to detect tau neurofibrillary tangles in the brain of patients being evaluated for AD [28].

CSF tests

CSF fluid protects the brain and spinal cord from injuries by providing cushioning effects and also supplies nutrients. In the early stages of AD, the CSF level of tau and beta-amyloid changes. CSF tests are very helpful in the diagnosis and detection of AD. Most of the research on AD biomarkers has been done on biological fluids like blood or CSF. The best method for identifying AD biomarkers is using CSF since this fluid directly contacts brain interstitial fluid and more accurately reflects metabolic alterations associated with CNS functions. Aβ (Aβ-42), phosphorylated tau (P-tau), and total tau (T-tau) are CSF biomarkers that are crucial for the diagnosis of AD. An increase in tau and phospho-tau (pTau) and a decrease in Aβ in CSF of AD patients is the most well-known and widely accepted molecular-based tissue fluid diagnostic for AD [29]. FDA has approved Lumipulse G an automated immunoassay to measure the biomarkers in the CSF of Alzheimer patients. Fujirebio Diagnostics, Inc. got FDA approval in May 2022 for Lumipulse G, an in vitro diagnostic test to detect amyloid plaques in CSF for early detection of AD. [30,31]. Another FDA-approved Test of AD is Elecsys® AD CSF assays by Roche. This method includes three assays viz, Elecsys β-amyloid CSF II, Elecsys phospho-Tau CSF, and Elecsys total Tau CSF [32].

Blood tests

Blood tests are used as cheap, easy, and simple diagnostic tools to diagnose a disease. Blood tests are used only in patients with memory complaints. Blood tests may detect tau, beta-amyloid, or other biomarkers before and after the disease. However, in AD blood tests are not approved by FDA [17]. The most encouraging findings to be released so far have examined CSF samples that were taken via lumbar puncture. However, less invasive procedures that analyze proteins in blood or urine may be able to assist primary care doctors in providing their patients with long-term prognostic advice. Nonetheless, a lot of biomarker scientists believe that creating a diagnostic test that

Table 1. Biomarkers for AD.

Biomarkers	Application	Advantages	Disadvantages	References
Brain imaging markers				
FDG-PET	A topographic biomarker to distinguish typical and atypical AD. Regional hypometabolism patterns are indicative of clinical impairments in all AD forms. Indicator of synaptic activity, neuronal function & neuronal metabolic activity of the brain.	Provides differential diagnosis. Can detect hypometabolism features of non-AD dementia like Lewy bodies and frontotemporal dementia	Relatively expensive and limited in availability Cannot directly detect the core pathological features of AD (Aβ & tau), not widely used.	[34–38]
Amyloid PET	The most widely tested biomarker for identifying amyloid plaques which has shown excellent accuracy in imaging-to-autopsy investigations (specificity: 100%; sensitivity: 92%).	An early detection biomarker that can identify localized Aβ deposits that may occur before the global neocortical signal turns pathological	Mostly utilized in a research context and only detects fibrillar or insoluble Aβ plaques in the brain, not other Aβ peptide types	[39–41]
Tau PET markers	Detect neurofibrillary tangles with more accuracy than fluid biomarkers accuracy.	More accurate predictor of cognitive decline than amyloid PET in cognitively intact people.		[42–44]
Synaptic vesicle glycoprotein 2A (SV2A) PET	Maybe a useful biomarker of synaptic density to monitor the course of AD	Contribute to the staging and prognostication of diseases.	not useful in differential diagnosis and less used in clinical studies	[45,46]
Single-structure MRI markers	indicates neurodegeneration by displaying grey matter atrophy and volume loss.	A simple method to detect AD in the early stages where it can be extremely challenging to diagnose.	Low molecular specificity, Difficult to detect atypical AD, can't detect the effect of amyloid beta plaque or NFTs in the brain.	[47]
Serial registered structural MRI	a potent technique to take several images (brain MRI) one after another for measuring brain atrophy to track the progression of AD	has less variation than a single structural MRI	Low molecular specificity, AD, can't detect the effect of amyloid beta plaque or NFTs in the brain.	[48]
Diffusion tensor imaging MRI	Uses anisotropic diffusion to evaluate axonal or white matter damage	Early detection of AD	very sensitive to movement; if the patient moves, misregistration may occur. DTI therefore needs a minimum of 7 tensor fits. -demands a significant amount of man-hours, knowledge, and computing power.	[49,50]
Resting-state functional MRI	To examine the brain's intrinsic networks at rest and evaluate the functional brain connectivity alterations that are assumed to precede the structural brain alterations. It uses blood oxygen level-dependent (BOLD) signals to measure neuron's synaptic activity.	Noninvasive with superior spatial resolution in comparison to alternative imaging methods	Individual changes in brain activity between the waking and sleep states are not yet well understood.	[51–53]
Task-related functional MRI	Measure BOLD signals during cognitive tasks performed by patients	Similar to resting stage MRI, task-related MRI can measure the short-term therapeutic response and identify early brain damage linked to AD.	Not feasible for severely impaired patients to perform cognitive tasks	[54]
T2-weighted or susceptibility-weighted imaging (SWI) or MRI	Early detection of cerebral amyloid angiopathy-linked microhemorrhages in patients with Alzheimer's type dementia	a new and more accurate way to clarify the apparent connection between cerebral amyloid angiopathy and microhemorrhages and Alzheimer's disease	not currently used in most clinical studies but may become more crucial to managing amyloid-related imaging problem	[55, 54,56,57]
CSF based biomarkers				
CSF Amyloid and tau protein biomarkers	CSF amyloid biomarkers are Aβ42, Aβ40 and tau biomarkers are phosphorylated tau (p-tau)-181, p-tau217 and total tau	detect biochemical alterations linked to AD, even in pre-symptomatic and prodromal stages of the disease's development, and have even shown the ability to forecast cognitive loss	quite expensive and needs highly specialized facilities and staff that are knowledgeable in this method.	[58]

(*Continued*)

Table 1. Continued

Biomarkers	Application	Advantages	Disadvantages	References
CSF tau	Measurement of tau proteins including total tau and p-tau in CSF, to evaluate AD. A more precise marker for Alzheimer's disease is p-tau. .	An alternative method to PET scan to accurately diagnose AD. As an indicator of neuronal death, it can be raised in both non-AD dementias and atypical phenotypes.	Quite expensive and needs highly specialized facilities and staff that are knowledgeable in this method.	[59]
CSF Amyloid	Abnormal amounts of CSF amyloid protein clump together to produce plaques in the Alzheimer's brain that impair cell function.	Provides a quantitative measurement of the overall effects of biomarkers.	Aβ-PET detects Aβ depositions in specific regions that may arise before the overall neocortical signal becomes pathological. High cost and not interpretational	[60]
CSF neurofilament light chain (NfL)	A potential biomarker of neurodegenerative disease, correlated with cognitive abnormalities	A highly sensitive method that can be used in place of total tau as a biomarker of neurodegeneration	Not specific biomarkers of a single neurodegenerative disease but used as general biomarkers	[61]
CSF- Chitinase 3 like 1 protein (CHI3L1/ YKL-40)	A potent biomarker that can be identified at the early stage of pathogenesis and aid in distinguishing AD from other types of dementia.	A potential preclinical biomarker in the prognosis of AD	not involved in differential diagnosis but rather in disease staging and prognostication.	[62]
CSF-Glial fibrillary acidic protein (GFAP)	An astrocyte biomarker for AD and other neurodegenerative diseases like Lewy body dementia and frontotemporal dementia	detect the current state of the disease and predict future developments	Non-specific neurodegenerative biomarker	[63,64]
CSF synaptic and postsynaptic (neurogranin) biomarkers	The level of the presynaptic proteins like Growth-associated protein-43 (GAP-43), Synaptosomal-associated protein-25 (SNAP-25) and synaptotagmin-1, and Neurogranin, a postsynaptic protein, are increased in AD.	Symptomatic AD can be accurately distinguished from other dementias	not involved in differential diagnosis but rather in disease staging and prognostication.	[65,66]
		Blood-based biomarkers		
Plasma amyloid, tau and other protein biomarkers	may indicate the existence of neurodegenerative illness, neuronal injury, or amyloid alterations in the brain	Plasma concentrations of p-tau and Aβ peptides correlate with PET-positive results and their corresponding CSF concentrations.	Should not be used as a stand-alone test to identify AD or any other dementia. But used in conjunction with other diagnosis techniques	[65,67]
Blood Apolipoprotein E (Apoe ε 4) gene biomarker	A recommended genetic biomarker for amyloid pathology and diagnosis of AD	a significant genetic risk factor for late-onset AD	Should not be used as a stand-alone test to identify AD or any other dementia. But used in conjunction with other diagnosis techniques	[68]
		Emerging biomarkers		
Retinal imaging	alterations in the eye may be associated with brain neurodegeneration, brain blood vessel damage, or other processes related to disease.	Retinal imaging might be a precise, non-invasive, and economical diagnostic tool.	Not used clinically	[69,70]
Saliva biomarkers	To determine amyloid and tau protein in saliva	A noninvasive and simple method	Not used clinically	[71,72]
Urine biomarkers	Detection of AD-associated proteins in urine	Easy, non-invasive and economical method	Nonreliable, not used widely	[33,73,74]

is sensitive and specific enough to be applied to urine or plasma samples will be extremely challenging, if not impossible [33].

VARIABILITY IN AD PATHOGENESIS

AD can have extremely diverse clinical presentations and pathological processes that vary greatly in severity, location, and composition. These variations include the amount and distribution of AB deposition and the spread of neurofibrillary tangles in different brain regions, which can lead to atypical clinical patterns and the emergence of unique AD variants. Variability in AD pathogenesis can adversely affect the diagnosis and treatment of AD. Variability in AD pathogenesis may be due to the presence of genetic, demographic, neuropsychiatric, and comorbidity-related factors [75]. APP processing and the significant amount of Aβ deposition brought on by individual mutations appear to be the primary initiators of the AD process,

according to genetic studies of autosomal dominant types of AD. Demographic factors such as age at onset, sex, race, and ethnicity influence the prevalence of AD. 3% of persons between 65% and 74%, 17% of persons between 75% and 84%, and 32% of persons above 85 years of age have AD. A higher prevalence of AD and other dementias is seen in women due to their longer average lifespans than males. There are well-established ethnic and racial disparities in the likelihood of getting Alzheimer-related disorders. Older Black/African Americans are twice as likely to develop Alzheimer-related disorders as older White people and older Hispanic/Latinos are roughly 1.5 times more likely [76,77]. Comorbidities such as hypertension, diabetes mellitus, liver diseases, and so on, can increase the risk for AD and add to the heterogeneity of AD. The neuropsychiatric inventory is often used to quantify neuropsychiatric symptoms (NPSs), and it has been suggested that NPS influences both the phenotypic heterogeneity and the rate of progression of AD. There may be biological heterogeneity in the disease as seen by variability in biomarker profiles across persons with dementia and mild cognitive impairment as well as cognitively normal individuals. In AD, blood-based (plasma) and cerebrospinal biomarkers are examples of fluid biomarkers. It is evident from these biomarkers that the pathophysiology of AD is heterogeneous [78].

CHALLENGES OF BIOMARKER-BASED DIAGNOSIS

Despite our knowledge about the amyloid and tau pathology, the complete picture of AD pathophysiology remains elusive. Additionally, to diagnosis, the available biomarkers for AD are ineffective in predicting the course of the illness and cannot be utilized to track patients' responses to immunotherapy using monoclonal antibodies against Aβ and tau or other currently being tested therapeutic modalities. Finding novel biomarkers that can also be used for these purposes is therefore extremely important. The limited therapeutic value of biomarkers, typically in elderly patients, is due to the extremely invasive (lumbar puncture) method of collecting CSF. This might make it impossible to use it for long-term investigations or clinical progression monitoring, both of which would require frequent CSF samples. The emphasis must be placed on standardizing the testing of these biomarkers due to the high inter-laboratory variation in the observed concentration of these biomarkers. Due to the heterogeneity of AD pathogenesis, potential AD CSF biomarkers should be looked at more thoroughly [13]. Blood-based biomarker assays are less invasive and more cost effective than alternative methods. These strategies are feasible to implement and offer repeated sampling in large cohorts, which makes them potentially superior to other biomarker modalities [13]. However, blood's complex makeup makes it challenging to employ as a matrix for assessing biomarkers [13]. The enormous dynamic range of proteins in blood is the most difficult of many challenges to the development of blood-based biomarkers. It can be difficult to identify blood changes that are particular to AD since blood changes are frequently very small and represent a wide range of peripheral and central processes. As the brain is separated blood-brain barrier, it is difficult to relate the analytes found in blood and the changes the in brain. However, the BBB gets disrupted with age and increases the brain's permeability. Therefore, the detection of protein-based biomarkers of AD in the blood is significant. However, blood levels of the most recognized possible biomarkers are far lower than those observed in CSF. For instance, the concentration of Aβ peptide in the blood is 100 times lower than that in CSF. Additionally, the presence of less abundant proteins that may act as potential biomarkers may be concealed by extremely abundant plasma proteins like albumin and IgG [13]. In addition to blood and CSF, other fluids, such as saliva, urine, and tear fluids, have also been studied in a few studies [3]. Analysis of the saliva of AD patients showed increased levels of proteins that are involved in homeostasis, ROS scavenging, neuroprotection, and antibacterial activities in comparison to control [79]. In contrast, proteins involved in gluconeogenesis, complement activation, and lipoprotein metabolism were changed in the urine of AD patients [80]. In the tear fluid, the Eukaryotic translation initiation factor 4E was present only in samples of AD individuals [81]. It has already been discovered that eukaryotic translation initiation factor 4E is elevated in the brain tissues of AD patients, and it may be involved in the mechanisms behind tau hyperphosphorylation [82].

CONCLUSION

Over the past few years, biomarker advancements have produced intriguing discoveries. Researchers can now monitor the beginning and course of AD, observe changes associated with the condition in living individuals, and assess the efficacy of promising medications and other possible treatments. Furthermore, new disease-modifying therapies for AD are currently being developed or authorized. Clinical trials are focused on individuals with early AD (mild cognitive impairment from AD or early AD dementia) making early AD diagnosis even more crucial. With the understanding of Aβ and tau pathologies and the subsequent discovery of CSF and neuroimaging biomarkers, new diagnostic, prognostic, and therapeutic options have become available leading to a better redefinition of AD. However, thorough characterization of the targeted biofluid or tissue samples is required for the identification, qualification, and validation of diagnostic and prognostic biomarkers, which demands the use of various approaches and instruments.

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All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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