



The most valuable biomarkers of Alzheimer's disease: A review article

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ABSTRACT

Alzheimer's disease (AD) is the most popular type of dementia in elderly and is described by a progressive loss of cognitive capacity and severe neurodegeneration which typically begins with memory deficits. The major biomarkers of AD include total tau, phosphorylated-tau and 42 amino acid isoform of amyloid beta that reflect neurodegeneration and indicate the pathophysiological processes in AD. Biomarkers have been analyzed in different kinds of body fluid. Cerebrospinal fluid (CSF) biomarkers are particularly valuable to discriminate early AD from other diseases associated with memory impairment. However, access to CSF is invasive and researchers try to find valuable biomarkers in other body fluids. In this article, we reviewed different kinds of biomarkers and their validity to diagnose and effectiveness in AD therapy.

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INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative condition specified by the formation of amyloid-plaques, aggregation and hyper phosphorylation of tau protein that ultimately result in behavior changes with a progressive loss of functional memory. AD has been characterized by decreased synapse density in hippocampus and neocortex. The severity of synapses diminution is related strongly to the stage of the disease [1, 2].

Pathophysiology of Alzheimer

The most common and typical pathological hallmarks in AD are senile plaques and neurofibrillary tangle (NFTs). These two lesions are caused by the dysfunction and accumulation of two proteins which are, respectively, the beta-amyloid peptide and the tau protein. The main pathogenesis of AD includes the formation and deposition of amyloid β ($A\beta$), NFTs (assembled by hyper phosphorylated

Tau protein), and inflammation [3, 4]. Fibrillary $A\beta$ plays an important role in AD pathogenesis through activation of microglia and stimulates the release of inflammatory mediators, which lead to neuronal dysfunction and subsequent cell death [5]. There are several hypotheses explaining the mechanisms involved in the pathogenesis of AD. Cholinergic discrepancies, $A\beta$ deposition and tau protein accumulation are the most powerful hypothesis involved in AD pathophysiology [6, 7]. This process is started by extracellular fibrillary β -amyloid accumulation, with following intra neuronal hyper phosphorylated tau protein aggregation [8]. Furthermore, synapse loss and neurodegeneration lead to memory impairment and other progressive neuronal degeneration [8, 9]. Recent studies have also emphasized on the role of $A\beta$ oligomers in synaptic impairment that is primarily the only one among several other signals destroys the integrity of

brain functions [7]. It has been detected that $A\beta_{42}$ oligomers induce oxidative damages and form toxic oligomers which help formation of plaques, increase tau hyperphosphorylation, and resulting in toxic effects on mitochondria and synapses. $A\beta$ is a fragment from a larger amyloid precursor protein (APP). APP is a transmembrane protein that enters through the neuron's membrane. APP has an important role in neuron growth, survival, and post-injury repair [10]. β - and γ -secretase mediated generation of $A\beta$ in AD, a proteolytic process which causes APP to be divided into smaller fragments [11, 12]. One of these fragments that pay rise to fibrils of amyloid beta is the primary component of amyloid plaques that is known as the senile plaques [13]. Tau protein stabilizes the microtubules when phosphorylated. In AD, chemical changes of tau protein begins to pair with other threads, creating neurofibrillary tangles and finally lead to disintegrate of the neuron's transport system [14]. Tau protein is mainly expressed in the neurons and has an important role in stabilizing microtubules, as the key components of axonal transport and in signal transduction. Tau alterations are observed in numerous neurodegenerative diseases. The phosphorylation of tau proteins reduces their affinity for microtubules that result in their instability that ultimately lead to disrupted axonal transport and synaptic

dysfunction. Normally, the six hyperphosphorylated brain tau isoforms (PHF-tau) are located mainly in axons, associated with the cytoskeleton and intracellular transport systems. Total tau (t-tau) and truncated forms of monomeric and phosphorylated tau (p-tau) can be measured in CSF. Total tau levels are significantly enhanced in AD patients. Tau is markedly hyperphosphorylated (39 possible sites) in AD, which causes a lack of function and axonal transport dysfunction. Expression of phosphorylated tau is significantly enhanced in people with Alzheimer's disease in comparison to controls.

Biomarkers

Biomarkers, also known as molecular marker and signature molecule [15], are measurable cellular, biochemical or molecular transformations observed in biological media such as human tissues, cells, or fluids that reflect a particular physiological state [16, 17]. Biomarkers are valuable for the risk determination of disease but are also invaluable in establishing a diagnosis and may be used to see how well the body gives reaction to a treatment for a disease or condition [15, 18]. In medicine, they are often insulated from serum, urine, or other fluids that can be used as a sign of the presence or intensity of a particular disease state. Biomarkers play critical role in the development of new drug therapies [19]. These molecules can take many different

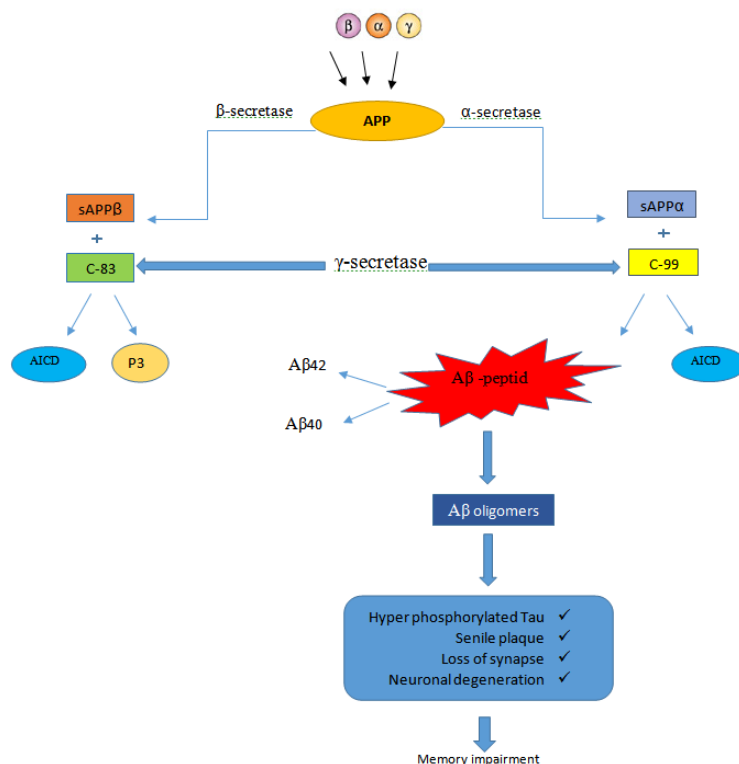


Figure 1. Diagrammatic representation of APP processing and $A\beta$ aggregation

There are two enzymatic pathways for cleavages of APP; α -secretase pathway that produces sAPP α and C83 (left boxes), and β -secretase pathway that produces sAPP β and C99 (right boxes). Carboxyterminal fragment C99 is cleaved by γ -secretase to generate $A\beta$ ($A\beta_{40}$, $A\beta_{42}$) and APP intracellular domain (AICD). Carboxyterminal fragment C83 also is cleaved by γ -secretase for the secreted peptides p3. $A\beta$ accumulation is also called oligomers. Oligomers cause loss of synapse, formation of senile plaque and ultimately memory impairment [7].

forms, including particular proteins or peptides (ovarian-specific antigen as an indicator of increased risk for ovarian cancer), antibodies (anti-citrullinated protein antibodies for rheumatoid arthritis), cell types (white blood cell counts in infection or cancer), metabolites (phenylalanine in urine of newborns with phenylketonuria), lipids (cholesterol and other lipid levels in cardiovascular disease), hormones (thyroid stimulating hormone in Hashimoto's disease), enzyme levels (various hepatic enzymes for liver cancer), physiological states such as blood pressure or fever, or imaging studies of particular organs or organ systems (neural degeneration in Parkinson's disease). A biomarker can also be a substance introduced into a patient to assess how internal organ systems are functioning, such as radioactive iodine used to measure thyroid function. Ultimately, biomarkers can be used to detect a change in the physiological state of a patient that correlates with the risk or progression of a disease.

Biomarker of Alzheimer's disease

An ideal AD biomarker should have the following criteria (i) ability to detect author fundamental features of AD neuropathology that can be validated at autopsy; (ii) ability to differentiate AD from non-AD dementias; (iii) ability to detect early stages of AD and differentiate the stages of AD progression to carry out an effective treatment; (iv) highly reliable, easy to perform, and inexpensive; and (v) use minimally invasive sample collection, such as from peripheral tissues without requirement for lumbar puncture or other invasive sampling procedures.

The pathological changes in AD brain result from cellular processes such as inflammation, oxidative stress, A β metabolism, tau phosphorylation, and APP. These pathological changes could be detected in biological fluids. Biomarkers in AD contain cerebrospinal fluid markers (CSF), brain imaging markers (PET and MRI neuroimaging markers), markers detected in peripheral tissues such as blood and skin and plasma (1-3). The validity of CSF AD biomarkers has been shown in the several studies of studies in all stages of AD [22-25].

CSF biomarkers

CSF is in direct contact with the extracellular space in brain and its proteins are restricted by blood-brain barrier.

Biochemical changes could be detected in CSF that reflects pathophysiological processes in the brain.

The pathological hallmarks of AD such as A β , T-tau, P-tau, can be measured in CSF by enzyme-linked immunosorbent assay. Identification of CSF biomarkers is very valuable to monitor the disease in the earliest stage to prevent progression of the disease [26].

CSF biomarkers for AD can be divided into basic and core biomarkers. Basic biomarkers have been used to diagnose inflammatory and infectious in central nervous system, such as, CSF cell count and the ratio of CSF/serum albumin which is used to monitor the blood brain barrier (BBB) and an increase has been indicated in AD with concomitant cerebrovascular pathology.

CSF core biomarkers include A β ₄₂ T-tau, and P-tau [22] that is useful to monitor AD diagnostics in early stage as well as the developed AD [8, 21, 27-29]. Many studies demonstrated that level of P-tau, T-tau and A β in CSF changes during AD progression. A low level of A β ₄₂ in CSF is a critical marker for cortical amyloid deposition in brain. The levels of CSF T-tau and P-tau proteins increase in AD and accelerate during later disease stages with neurofibrillary tangle accumulation [4, 26, 28-34].

Neuronal imaging biomarkers

Different kinds of neuroimaging methods can be principally classified as structural and functional biomarkers. The main structural imaging techniques are computational tomography (CT), magnetic resonance imaging (MRI) and functional neuroimaging techniques including: functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT) [30]. Neuroimaging biomarkers of mild cognitive impairment can be diagnosed in preclinical stages of AD. These techniques have been developed to provide evidence for A β deposition, tau aggregation and neurodegenerations at the early stages of the disease [20, 31, 32]. The two types of neuroimaging most commonly used as AD biomarkers are PET and MRI. There are two types of PET; a) amyloid tracers that determine pathological A β by employing radio ligands such as C-Pittsburgh compound B and florbetapir, which bind to fibrillar amyloid plaques [33, 34], b) Fluorodeoxyglucose (FDG) which evaluates brain metabolism. MRI is one of the non-invasive imaging

Table 1. Blood markers observed in Alzheimer's disease patients blood samples

<i>Biomarker</i>	<i>Blood plasma/serum</i>
Tau-total	Significantly changed/considerable variability between studies
total A β and A β ₁₋₄₂	Elevated in AD
Albumin ratio	Marginal effect/slightly higher in AD
Vwf	Significantly elevated in AD
Cortisol	Significantly elevated in AD
OLAB	Significantly decreased in AD
GSK-3	Elevated in early-stage AD
PKC	Decreased in AD
Annexin A5	Increased levels in the plasma of AD

AD, Alzheimer's disease; A β , amyloid- β ; Vwf, von Willebrand factor; OLAB, oxidized LDL antibodies; GSK-3, glycogen synthase kinase-3; PKC, protein kinase C.

Table 2. Peripheral markers

<i>Tissue and liquids biomarker</i>	<i>Abnormalities</i>
Skin fibroblasts	Reduced levels of PKC ϵ
Skin fibroblasts	Unfolded P53 expression at the basal level
Skin fibroblasts	A β secretion is elevated
Skin fibroblasts	Dysfunctional Erk1/2 signaling
Eye lenses	Cytosolic A β deposition
Saliva	A β 42 levels are significantly elevated in early stage AD
Urinary	increased levels of KLK1, Kallikrein-6, GALC, Ceramide CERU

AD, Alzheimer's disease; A β , amyloid- β ; PKC, protein kinase C; Erk1/2, extracellular signal-related kinases 1 and 2; KLK1, Kallikrein-1; GALC, Galactocerebrosidase; CERU, Ceruloplasmin

techniques for the structural analysis and investigation of neurodegeneration that is widely applied in clinics and research [2]. MRI is a useful method to characterize the functional abnormalities in different kinds of dementia. It measures the oxygen concentration of certain specific brain areas corresponding to particular stimuli or cognitive tasks. Most of MRI studies demonstrated that atrophy of the medial temporal lobe structures (hippocampus, and entorhinal cortex) is common in AD [30]. Advanced MRI techniques, which are called structural magnetic resonance imaging (sMRI), are used to show atrophy in white matter and cortex [32]. fMRI studies show that patients with AD have lesser-coordinated activity in the hippocampus, inferior parietal lobes and cingulate cortex compared with healthy controls [30].

Blood biomarkers

Today, several metabolites and proteins have been recognized as potential biomarkers in plasma and serum of patients with AD such as brain-derived neurotrophic factor (BDNF) stromal cell-derived factor 1 (SDF-1), Granulocyte - colony stimulating factor (G-CSF), alpha-2-macroglobulin, apolipoprotein A-I, various markers of inflammation (like; Interleukin -6, tumor necrosis factor- α , interleukin-1 β), complement factor H (CFH) precursor and a-2-macroglobulin (α -2M), markers of oxidative stress (homocysteine, isoprostanes) and total cholesterol A β [31, 35-38].

Majority of A β present in plasma is bound to albumin and there is a high concentration of tau in plasma of people with Alzheimer disease. T-tau and p-tau are established markers for diagnosing AD in CSF, while tau levels in blood have not been investigated [39]. In familial AD cases, total A β and A β 1-42 plasma levels are elevated [40].

Protein kinase C (PKC) has been considered as a blood biomarker in AD (Table 1). PKC has an important role in memory and synapse formations and its signaling pathways disrupts in patients with AD [16].

Glycogen-synthase kinase-3 (GSK-3) as other blood biomarker, involves in the hyper-phosphorylation of Tau and the increased production of beta-amyloid. High levels of GSK-3 has been sampled in the white blood cells in the early stages of AD [40]. The level of cortisol, von Willebrand factor and oxidized LDL antibodies could differentiate AD

cases from healthy controls with over 80% accuracy [41]. Annexin A5 was reported to be a biomarker of AD and present at increased levels in the plasma of patients with AD [42].

Other biomarkers

Anatomical Markers

Anatomical markers of AD are cerebral atrophy and macroscopic vascular alterations. The brains from AD patients are characterized by a severe atrophy leading to dilation of the ventricular system and a widening of cortical sulci [21]. In the early stages of the disease, the atrophy process affects mainly medial temporal areas including the hippocampal formation. In AD, amyloid proteins accumulate in the periphery of blood vessels that result in cerebral amyloidangiopathy (CAA).

Pathophysiological marker

Many types of biological biomarkers were mostly selected based on our knowledge of the pathophysiology of AD, for example biomarkers of neuro-inflammation (cytokines, complement C3, matrix metalloprotease), oxidative stress (α -aminobutyric acid, DNA oxidation, superoxide dismutase, [42, 43] and lipid metabolism (apolipoproteins).

Peripheral markers

The Amyloid pathogenesis and tau metabolic pathways have been indicated in the peripheral tissue like in the blood, saliva, skin, and other peripheral tissues (Table 2). A β deposition has also shown in the lens as well as blood cells, blood vessels, skin, subcutaneous tissue, and intestine of patients with AD.

The fast collection of peripheral fluids and process of analysis consider important advantages of biomarkers. The collection of saliva, urine, fibroblasts, or eye secretions is more fast, cheap and noninvasive than blood. However, these fluids are not sensitive to detect low-level [44].

DISCUSSION

Today, biomarkers used most widely in the clinical trials for dementia [25, 45, 46]. Some extent biomarkers in clinical practice are measurement of A β in CSF, imaging of metabolism using (FDG)-PET, structural MRI and molecular

imaging of amyloid deposition using PET. The ideal biomarker for AD should have sensitivity more than 85% for detecting AD and a specificity more than 75% for differentiating AD from non-AD dementias [20]. It should also be able to provide an earlier diagnosis of AD or assess the risk of developing AD. Structural MRI and FDG-PET do not directly measure the core biomarkers of AD (A β and tau proteins) and may be considered as the nonspecific biomarkers for AD monitoring.

Extensive evidences suggest that CSF biomarkers have high sensitivity and specificity for diagnosis and monitoring of Alzheimer brains [3, 20, 27, 47-53]. Since CSF is in direct contact with the extracellular space in brain, it could reflect biochemical changes in the brain more specifically and sensitive than other biological fluids such as plasma/serum or urine. Among CSF biomarkers A β 1-42 is the most sensitive biomarker for AD [54-55]. The level of T-tau protein is about 300% higher in AD patients than control subject [53, 54], but this biomarker is not specific for AD. The high level of T-tau protein can be found in CSF of patients who have suffered from acute stroke or head trauma [54, 55]. P-tau protein may have a greater value since it is specific for AD. Neuroimaging biomarkers have potential to predict the transition from mild cognitive impairment to AD [21, 35]. Currently, the most promising approach to diagnosing AD is the combination of multiple biomarkers. Collection of CSF is an invasive procedure, therefore, development of new methods and identification of blood-based biomarkers are needed.

Blood biomarkers of AD provide a cost and time effective way to improve the use of CSF and neuroimaging biomarkers. In addition to measuring of biomarkers, blood collection and availability are easier than CSF [56]. However, the BBB can complicate the measurement of biomarkers in plasma, because of limitation of the proteins transportation. An important defect of blood biomarkers and neuroimaging methods is that their reliability is not the same as CSF biomarkers. Although the efficacy of CSF biomarkers is incredible, the invasive method of samples gathering motivates researches to find more reliable and non-invasive methods.

CONCLUSION

There is a clear need for the development of a simple, inexpensive, minimally invasive test for AD to diagnose the disease, ideally at the earliest stages, to predict and monitor progression and therapeutic efficacy. Discovery and development of ideal AD biomarkers may also lead to the identification of new therapeutic targets and approaches. Use of neuroimaging and CSF biomarkers provide new insights into brain organization and enable the detection of specific proteins and/or protein aggregates associated with AD. Combinations of AD biomarkers into a molecular signature or index may prove to be more accurate than any single biomarker.

CONFLICT OF INTEREST

The authors declare that this research does not have any conflict of interest with anyone or any Institute.

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