

The Status and Development of Biomarkers of Alzheimer's disease

Amelia Huang *

Shanghai Foreign Language School, Shanghai, China

* Corresponding Author Email: amelia.huang@uwantgroup.com

Abstract. Alzheimer's disease (AD) is an extremely familiar form of the dementia. After the age of 65, the likelihood of developing Alzheimer's disease increases significantly. However, because the pathogenesis of AD is insufficiently clear, intervention and treatment at an early stage is particularly critical. Since 2011, biomarkers have officially become the standard for diagnosing Alzheimer's disease. Potential biomarkers carry out a significant role in clinical, studies and other areas. Although the cerebrospinal fluid (CSF), also the positron emission tomography (PET) are effectual in detecting neurodegenerative processes at an early clinical stage, they are widely unused in the clinic due to their high cost and invasiveness. Plasma biomarkers are expected to be a more convenient and inexpensive diagnostic modality. In this review, biomarkers based on individual pathological findings are summarized in three main categories: PET, CSF, and plasma. The paper outlines the development and application of biomarkers to date and mentions the challenges that still need to be addressed.

Keywords: Alzheimer's disease, biomarkers, CSF, PET, plasma.

1. Introduction

Alzheimer's disease (AD) is a degenerative form of dementia, so far, the disease has affected more than 50 million people worldwide, and the number is expected to reach 150 million by the 2050. It is always described as a gradual decline in one's intellect, behavior, and social skills, decreasing one's ability to function independently. The prevalence of neurodegenerative dementia in AD ranges from 50 to 70% [1]. People above the age of 65 have an extremely high frequency of Alzheimer's disease. The incidence increases exponentially after the age of 65.

Alzheimer's disease's specific pathophysiology is uncertain. One of the most commonly accepted hypothesis is the amyloid cascade hypothesis. The neurodegenerative process is thought to have begun 20-30 years before symptoms appeared. Therapeutic intervention at the onset of symptoms will be extremely effective because it will prevent the progression of synaptic damage and neuronal loss. Scientists have combined AD-specific indicators for diagnosis, such as A and tau deposition, glucose hypometabolism, and brain shrinkage, it is used to detect suspected signs of the disease at an early stage. Different biomarkers are suggestive of different AD processes and stages. It is critical to create biomarkers capable of detecting these changes in order to enhance the possibility of monitoring and treating the underlying cause.

The Alzheimer's Disease and the Related Disorders Association (ADRDA) and the National Institute of Neurological and Communication Disorders and Stroke (NINCDS) organized a research team in the fall of 1983 to develop criteria and characterize the clinical diagnosis of this case. This report was issued in July of 1984. The standards outlined in the paper have been in use for almost 27 years. These criteria are frequently used in research trials and clinical studies for diagnosing possible Alzheimer's disease. However, after 27 years, the number of clinical cases has grown, and some criteria must be revised. Despite economic constraints in clinical application, the use of biomarkers is warranted in select circumstances, which are virtually always connected with the emergence of clinical symptoms. The use of biomarkers in medical practice has resulted in major improvements in therapeutic approaches for patients, especially in cases when disease-modifying medications are not yet accessible. An essential part of this is the integration of biomarkers into the diagnostic standards for AD and MCI.

This article will summarize the classic and newly discovered AD biomarkers in recent years, and describe the new detection technologies developed for some biomarkers.

2. Biomarkers corresponding to different stages of AD

2.1. Biomarkers for β -amyloid pathology

Beta-amyloid ($A\beta$) is an important part of amyloid plaques related to AD. The orderly breakdown of the β -amyloid precursor protein (APP) produces it. APP and Beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) are found together in the endosome, which is the location of intracellular $A\beta$ synthesis [2]. APP processing dysregulation can promote the pathogenesis of AD by boosting $A\beta$ production while decreasing the ratio of $A\beta_{40}/42$ [3]. When $A\beta$ aggregates into larger amounts of oligomers and protofibrils, it affects cellular function in a variety of ways, including impaired and lost synaptic activity, impaired cerebral capillary blood flow, and tau lesions.

$A\beta_{1-42}$ (the 42 amino acid type of amyloid) in the cerebrospinal fluid (CSF) has long been recognized as a key indicator of AD. Mass spectrometry can determine the concentration of $A\beta_{42}$ in cerebrospinal fluid (CSF) [4]. The finding of the relatively lower levels of the $A\beta_{42}$ in the CSF of the participants of AD was thoroughly verified and replicated in numerous investigations. This decline shows $A\beta_{42}$ segregation in aged brain plaques. Reduced $A\beta_{42}$ levels have been found in CSF of patients with moderate cognitive impairment (MCI) besides the preclinical phase of AD. Reduced $A\beta_{42}$ concentrations in cerebral fluid are similarly associated with plaque pathology in DLB. The results of a [11] $CPiB$ PET and CSF examination of 30 patients with possible Alzheimer's disease revealed that cerebrospinal fluid $A\beta_{42}$ concentrations may not only be a sign to subjectively distinguish persons with AD from healthy individuals, but also an involved a number of β -amyloid pile in AD, however this link is relatively strong.

Extra-pathological variables in Alzheimer's disease may impact plasma $A\beta$ concentrations. Although reports have found a link between plasma $A\beta$ concentrations and brain β -amyloidosis, these findings should be interpreted with caution. Furthermore, studies do not currently provide a molecular explanation for these correlations.

Pittsburgh compound-B (PiB) is a chemical probe that targets amyloid PET. This probe is detected in the cortices of AD patients and serves as reference locations in the cerebellum. Many scientific investigations have now corroborated the rising reserve of PiB in cerebral cortical regions of AD sufferers [5]. ^{18}F -florbetaben (Neuraceq), ^{18}F -flutemetamol (Vizamyl), and ^{18}F -florbetapir (Amyvid) are all clinically authorized for use, all of which showed positive association with amyloid plaque load in autopsy correlation, and despite the lack of pathological specificity of cerebral hypometabolism detected by [18] FDG PET compared with ^{11}C - PiB . As a result, a multi-biomarker strategy is advised to add further data to support categorization of individuals whose diagnosis is unknown [6].

2.2. Biomarkers for tau pathology

Numerous studies have found that hyperphosphorylated tau aggregation is a main cause of neurodegeneration in AD. Clinical neuropathology investigations indicate that tau pathology spreads in a characteristic fashion throughout the AD brain's neural connection network. In contrast to $A\beta$, the stage of tau pathology is closely related to the evolution of the cognitive anomalies. Primary age-related tau pathology (PART) occurs with aging even when cognitive function does not diminish. These observations have led to the concept that the initiation and propagation of tau pathology is principally responsible for cognitive loss and neurodegeneration in Alzheimer's disease.

Phosphorylated tau is secreted from neurons with tangles and can be detected specifically by ELISA. Another suggestion is that the rise in CSF P-tau is a pathogenic change unique to AD, as it is more apparent in AD than that in other tau lesions. P-tau in CSF has now been thought to be the most specific biomarker for this disease talking about in this article. With the exception of herpetic encephalitis and CNS surface iron deposition, this biomarker is not associated with any other disease.

Recent research has linked changes in soluble P-tau (cerebrospinal fluid and plasma) to A β accumulation and discovered that changes in the former occur before tau aggregation in AD detected by PET.

Still no validated blood biomarkers of neurogenic fibrillary tangle pathology have been found. Recent research, however, has found higher quantities of P-tau in neuron-derived exosomes in blood [7]. Exosomes are separated from plasma using antibodies, subjected to a series of treatments, and then their tau levels are determined by immunochemical methods. Despite its novelty, this technique indicates the ability to measure P-tau in blood. Another study suggests that tau content in CSF encompassing the upstream domain of MTBR may reflect pathological tau alterations happening in AD. It may be exploited as a biomarker for establishments of tau-targeted treatments for Alzheimer's disease tracking. It was also found that in JNPL3 transgenic (Tg) mice indicating the human tau mutation, the expression levels of t-tau and p-tau in NEX increased with the development of neuropathy, suggesting that tau proteins enter the circulation via exosomes. Because exosomes can cross the blood-brain barrier, tau proteins collected from plasma in neuronal cell-derived exosomes (NEX) could coincide more closely with brain tau levels and clinical symptoms. Finally, tau protein in serum is expected to be a valuable biomarker for monitoring AD development [8].

To visualize tau inclusion bodies in patients, PET tracers have been produced. F-AV1451, one of these probes, binds to tau inclusion bodies in AD patients, differentiating them from healthy controls and associating them with various local abnormalities of brain metabolism.

2.3. Biomarkers for the axonal degeneration

Axonal degeneration is an important hallmark of the Alzheimer's disease. In neurodegenerative diseases, axons degenerate much more slowly than in acute axonal degeneration. This offers the possibility of targeting degenerative axons as an early intervention therapy [9]. Indeed, several models suggest the appearance of neurodegeneration is accompanied by the onset of the toxic phase in the pathogenesis of AD [10].

T-tau (specific total tau) can be used to assess axonal degeneration or damage in AD [11]. T-tau concentrations rise in AD patients' cerebrospinal fluid. The greater the increase in tau concentration leads to a more severe neurodegenerative process. Nevertheless, increased T-tau levels in cerebral fluid are not exclusive to AD.

According to recent studies, T-tau and NF-L CSF assays are reconstructed as ultrasensitive blood assays utilizing Simoa technology [12]. The levels of the NF-L in serum and plasma coincide with those in the CSF. Most CSF assays are reproducible in blood. From the Alzheimer's Disease Neuroimaging Initiative (ADNI), a data which consisted 244 subjects between the ages of 55 and 90 years, was classified by lumbar puncture, magnetic resonance imaging, and simple mental status examination. In the cerebrospinal fluid and plasma of AD, the NFL showed a significant increase. Although NFL is elevated in other neurodegenerative diseases, there are some limitations, such as its specificity for diagnosing AD is not high, however, it is relatively accurate in diagnosing AD compared to T-tau in the CSF [13]. There is also evidence that in MCI subjects, higher CSF NFL concentrations are associated with the degree of brain atrophy. Therefore this can also be detected by relevant brain examinations. These findings suggest the possibility of NFL as a biomarker for AD. It has been reported that NAD⁺ carry out a significant role in the mechanism of axonal degeneration and is significantly reduced during aging [14]. Because NAD is important for ATP production, a decrease in NAD impairs energy production, resulting in axonal degeneration. However, the function of NAD⁺ in AD is unknown. Nevertheless, with AD, the process of axonal loss begins at an early stage, providing an ideal chance for diagnostic treatment, and it is especially crucial to investigate the processes of axonal degeneration to identify relevant therapeutics.

2.4. Biomarkers for neuroinflammation

Aside from β -amyloid and Tau pathology, another histological marker of Alzheimer's disease is neuroinflammatory responses. Neuroinflammation manifests itself in gliosis. Abnormal activation of

microglia and astrocytes can be used as one of the risk factors to identify the development of AD, and its inhibition of pro-inflammatory cytokine production may halt the growth of the disease. Under neuroinflammatory circumstances, microglia-driven IL-1, TNF, and C1q production has been demonstrated to encourage the creation of a neurotoxic subset of reactive astrocytes known as A1. Microglia use phagocytosis to sample, detect, and eliminate debris or apoptotic neurons, but this capacity is greatly diminished in a pro-inflammatory environment. The observations in the AD brain show that enhanced toxic function and loss of physiological characteristics may contribute to reactive astrocytes' detrimental consequences in AD.

The most commonly investigated neuroinflammatory item in PET is the mitochondrial 18 kDa transport protein (TSPO) [15]. And the outer mitochondrial membrane of steroid-synthesizing neurons in the central nervous system mostly expresses TSPO. TSPO was reported to be raised in both AD patients and animal models of the disease [16]. Given that TSPO is produced in cells other than glial cells, new imaging biomarkers with improved sensitivity and specificity in detecting neuroinflammation are needed. With highly selective ligands, new biomarkers should be almost entirely expressed in microglia or astrocytes, allowing for in vivo imaging assessment. Suitable receptor probes have been produced in animal models and tested in vivo, which should lead to commercially viable receptor probes.

3. Limitation

Biomarkers are defined as "measurable and assessed features that serve as indicators of normal biological systems, clinical, or pharmacologic reactions to treatment modalities." [17] Thus, biomarkers for Alzheimer's disease should represent the key pathogenic features in the brain, such as plaque and tangle pathology, in addition to the associated pathophysiological mechanisms, for example, the axonal and also the synaptic degeneration.

This "overview" study looked at three key biomarker modalities. CSF, blood, and PET all have different abilities to detect changes in the brain. CSF is the fluid closest to the brain, but it is more difficult to acquire because a lumbar puncture is required. It is a more expensive approach in the case of PET. A radioactive probe is also put into the patient's blood. The probe can pass the blood-brain barrier and stay on the target lesion indefinitely. As a result, this approach is also regarded as invasive. Prospective studies of diverse neurodegenerative illnesses are required to compare different biomarker patterns and determine whether a marker is a strong indicator of disease severity than another. In blood testing, one indicator appears to be promising. It has been demonstrated that NF-L is highly linked with cerebrospinal fluid and plasma/serum. For this specific protein, cerebrospinal fluid and blood testing offer nearly identical information. More research is required to replace relevant CSF or PET testing in other blood tests. To enable the application of fluid- and imaging-based biomarkers in clinical practice, measurement processes must be highly standardized and offer consistent results over time.

Individual potential biomarkers, such as amyloid PET, have different limitations: (a) amyloid PET alone cannot yet determine the causality of -amyloid plaques, (b) non-AD individuals (e.g., those with Lewy body dementia) can also have positive amyloid PET scans, and (c) lack of concordance with A plaque stages determined by pathological histological methods [18]. The unusual sensitivity to single nucleotide polymorphisms (SNPs) in the TSPO genome is a drawback of numerous generations of TSPO tracers. Researchers are looking for unaffected tracers [19]. Also, CSF NFL is not an AD-exclusive function. Increased levels, on the other hand, are detected in many neurodegenerative disorders. As a result, in the future, plasma NFL could be utilized as a diagnostic test at the initial clinical assessment of persons with memory loss. Plasma NFL could be utilized as a simple, noninvasive, and low-cost screening method in this case, primarily to rule out neurodegeneration. Although CSF biomarkers have many advantages such as specificity and sensitivity, they are costly and invasive to sample for clinical diagnosis. Therefore, in comparison, plasma biomarkers will become a more convenient and clinically appropriate diagnostic basis.

4. Conclusions

This review outlines several biomarkers that may allow early detection of Alzheimer's disease, depicts the pathological features corresponding to the different biomarkers, and summarizes the limitations of the different biomarkers.

The ratio of A β 42 and A β 42/40 in cerebrospinal fluid is a relatively early positive indicator in the clinical course of the AD. Over a clinically relevant time period, P-tau and also the T-tau levels in CSF are better indicators of cognitive symptom development than A β 42 (1-2 years). High levels of CSF neurogranular proteins appear to be exclusive to AD and unaffected by the majority of other neurodegenerative illnesses. Blood testing may be useful for screening in the future, allowing patients to be chosen for further diagnostic investigation in specialized clinics. Distinct biomarkers have different limitations and properties.

Biomarkers, brain imaging and therapeutic diagnostics, and artificial intelligence are considered to be the future of Alzheimer's disease management. Given the existing obstacles and accomplishments, early intervention and primary prevention will be a watershed moment in Alzheimer's disease research. There was a remarkable increase in report on AD biomarkers during the last 20 years. Hundreds of the clinical neurochemical studies have investigated the core biomarkers of AD cerebrospinal fluid, P-tau, A β 42, and T-tau, and the results have been relatively consistent. This indicates that these markers are not only highly accurate in the diagnosis of AD dementia, but also relatively reliable in the diagnosis of AD prodrome symptoms. These biomarkers have been standardized, and newer versions of the assays performed on fully automated devices have demonstrated outstanding analytical performance with little intra- and inter-laboratory variability. Several immunoassays based on these biomarkers are now commercially accessible. Now that fundamental AD biomarkers have been included in research diagnostic criteria, it is envisaged that the usage of these diagnostic tests in ordinary clinical practice will rise. New biomarkers have been added to the AD biomarker toolbox, reflecting further possibilities in AD pathophysiology. Increased use of AD biomarkers in clinical practice, as well as better identification of distinct phenotypes, could lead to earlier diagnosis, timely treatment, and appropriate support. In various investigations, several biomarkers associated with various illnesses have shown various possibilities. Despite the limits of some biomarkers, they are important tools for the detection and treatment of AD.

There are currently no efficient Alzheimer's disease therapies, possibly because the majorities are for those with advanced Alzheimer's disease. Despite significant literature support, no single case of cure has been reported. This highlights the need of intervening early in the progress of this case. Despite the fact that CSF biomarkers have not only the higher sensitivity but also the specificity for diagnosis, clinical use of blood biomarkers is preferred due to the less dangerous nature of blood collection. It is hoped that more biomarkers will be identified and tested in clinical trials in the future, as well as more convenient and affordable testing methods, to enable early identify Alzheimer's disease and successful treatment of this increasingly widespread neurodegenerative disease.

References

- [1] Scheltens P, De Strooper B, Kivipelto M, Holstege H, Ch  telat G, Teunissen CE, Cummings J, van der Flier WM. Alzheimer's disease. *Lancet*. 2021 Apr 24; 397(10284): 1577-1590.
- [2] Long JM, Holtzman DM. Alzheimer Disease: An Update on Pathobiology and Treatment Strategies. *Cell*. 2019 Oct 3;179(2):312-339.
- [3] Guo T, Zhang D, Zeng Y, et al. Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer's disease. *Mol Neurodegener*. 2020 Jul 16;15(1):40.
- [4] Kuhlmann J, Andreasson U, Pannee J, et al; IFCC Working Group on Standardization of CSF proteins (WG-CSF). CSF A β 1-42 - an excellent but complicated Alzheimer's biomarker - a route to standardisation. *Clin Chim Acta*. 2017 Apr; 467:27-33.
- [5] Blennow K, Mattsson N, Sch  ll M, et al. Amyloid biomarkers in Alzheimer's disease. *Trends Pharmacol Sci*. 2015 May;36(5):297-309.

- [6] Librizzi D, Cabanel N, Zavorotnyy M, et al. FDG PET/CT Imaging on the Management of Patients with Dementia. *Molecules*. 2021 Feb 26;26(5):1282.
- [7] Winston C N, Goetzl E J, Akers J C, et al. Prediction of conversion from mild cognitive impairment to dementia with neuronally derived blood exosome protein profile[J]. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease*
- [8] Huang LC, Chen MH, Chuu CP, Li KY, Hour TC, Yang YH. Plasma biomarkers and their correlation in adult children of parents with Alzheimer's disease. *Front Aging Neurosci*. 2022; 14:977515. Published 2022 Aug 30.
- [9] Lingor P, Koch JC, Tönges L, Bähr M. Axonal degeneration as a therapeutic target in the CNS. *Cell Tissue Res*. 2012 Jul; 349(1): 289-311.
- [10] Jack CR Jr, Holtzman DM. Biomarker modeling of Alzheimer's disease. *Neuron*. 2013 Dec 18;80(6):1347-58.
- [11] Olsson B, Lautner R, Andreasson U, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *Lancet Neurol*. 2016 Jun;15(7):673-684.
- [12] Andreasson U, Blennow K, Zetterberg H. Update on ultrasensitive technologies to facilitate research on blood biomarkers for central nervous system disorders. *Alzheimers Dement (Amst)*. 2016 Jun 25; 3:98-102.
- [13] Chen Y, Theriault J, Luo J, Ba M, Zhang H, Initiative ADN. Neurofilament light as a biomarker of axonal degeneration in patients with mild cognitive impairment and Alzheimer's disease. *J Integr Neurosci*. 2021 Dec 30; 20(4): 861-870.
- [14] Huang L. K., Chao S. P., Hu C. J. (2020). Clinical trials of new drugs for Alzheimer disease. *J. Biomed. Sci*. 27: 18.
- [15] Laurent C, Buée L, Blum D. Tau and neuroinflammation: What impact for Alzheimer's Disease and Tauopathies? *Biomed J*. 2018 Feb;41(1):21-33.
- [16] Zhou R, Ji B, Kong Y, et al. PET Imaging of Neuroinflammation in Alzheimer's Disease. *Front Immunol*. 2021 Sep 16;12.
- [17] Strimbu K, Tavel JA. What are biomarkers? *Curr Opin HIV AIDS*. 2010 Nov;5(6):463-6.
- [18] Thal DR, Beach TG, Zantette M, et al. Estimation of amyloid distribution by [18F] flutemetamol PET predicts the neuropathological phase of amyloid β -protein deposition. *Acta Neuropathol*. 2018 Oct; 136(4): 557-567.
- [19] Edison P, Brooks DJ. Role of Neuroinflammation in the Trajectory of Alzheimer's Disease and in vivo Quantification Using PET. *J Alzheimers Dis*. 2018;64(s1): S339-S351.