(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 5, Issue 4 , Page No: 279-288
July-August 2022

IJMSCR

Biological Markers for Alzheimer's Disease (AD)

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Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

Due to the difficulties in establishing an early diagnosis of Alzheimer's disease (AD), biomarkers that represent the illness's fundamental pathology are required. The levels of total Tau (t-Tau), phosphorylated Tau (p-Tau), and beta-amyloid peptide (Aβ42) in cerebrospinal fluid (CSF) are regarded as surrogate indicators of Alzheimer's disease (AD) pathogenesis. The combination of low Aβ42 and elevated levels of T-tau and P-tau can reliably identify early-stage AD patients, even before the onset of dementia. The combined study of imaging, CSF, and blood-based biomarkers is also helpful for distinguishing between Alzheimer's disease and other degenerative dementias and the precision treatment. The evolution of these CSF biomarkers has resulted in a unique illness diagnosis. The discovery of a unique clinical phenotype coupled with *in vivo* proof of pathophysiological markers allows for an exact diagnosis of AD prior to the onset of dementia.

Keywords: Alzheimer's Disease, Biological markers, β-amyloid (Aβ) peptide, neurofibrillary tangles (NFT)

Introduction

Alzheimer's disease (AD) was found as the most generally common neurodegenerative disease (1). Neurodegeneration is predominantly related to pathological amyloid-beta oligomers, intra-neuronal neurofibrillary tangles and protein aggregates (1, 2). In addition, there were regionally specific reductions in cerebral glucose metabolism, synaptic dysfunction, and mitochondrial dysfunction (3, 4). Also, the information above is composed of hyperphosphorylated microtubule-associated protein Tau (4). The development of AD goes through three specific stages: the first stage which is pre-symptomatic stage, the second prodromal stage of mild cognitive impairment (MCI), and the third clinical form of AD. AD accounts for approximately 50%–70% of cases that are well known in the area of neurodegenerative dementia (5). Worldwide the estimation of people who have dementia is a staggering 44 million cases (6). This number could still be able to triple by 2050 due to an aging population worldwide (7). Clinically, AD is defined by the decline of memory and cognitive function (8). In addition, most patients suffer from behavioral and psychological symptoms of dementia such as depression, over-activity, psychosis or aggressive behavior (9). Histological features of AD are senile plaques, which are made up of accumulations of β-amyloid (Aβ) peptide, and neurofibrillary tangles (NFT), These are fibrillar deposits of hyperphosphorylated Tau protein (p-Tau) (10). Other pathological events that seem to play a key role in the disease include synaptic dysfunction, inflammation or vascular dysregulation (11). An accurate diagnosis of AD is currently standing as one of the most difficult and challenging in all of clinical neurology (12). AD is typically diagnosed using an integrated knowledge and assessment of multiple biomarkers and interrelated factors. These assessments include personal information of the patient such as age, gender, lifestyle, medical and genetic information, and cognitive, physical, behavioural and geriatric

examination (13). Also, laboratory assessments of biofluids of the patients were evaluated, especially within the systemic circulation and cerebrospinal fluid (CSF) (14-16). Furthermore, multiple neuroimaging modalities of the brain have been analysed; this includes the limbic system, retina, and post-mortem neuropathological examination (8, 17). More often than not, prospective AD cases are accompanied by other progressive, age-related dementing neuropathologies including, predominantly, a neurovascular and/or cardiovascular component, multiple-infarct dementia (MID), frontotemporal dementia (FTD) and/or strokes or 'mini-strokes' often integrated with other age-related neurological and non-neurological disorders including cardiovascular disease and cancer (17). While a wealth of genetic, neurobiological, neurochemical, neuropathological, neuroimaging and other diagnostic information obtainable for a single AD patient can be immense (18, 19). It is currently challenging to integrate and formulate a definitive diagnosis for AD from this multifaceted and multidimensional information (17, 20). These data are unfortunately not directly comparable with the etiopathological patterns of other AD patients even when carefully matched for age, gender, familial genetics, and drug history (4, 21). After four decades of extreme AD research have indicated that diagnostic profiles for AD show an extremely heterogeneous neurological disorder (17, 22). This research aims to give us a brief explanation of how Alzheimer's disease can affect a patient in the short term and long term whether in a bad way or not. It also gives specific details and examples of symptoms or other behavioral aspects that come from Alzheimer's disease.

General overview of different types of biomarkers

Being able to identify the different types of biomarkers in AD can really help understand each biomarker better (23). One important point to know is the feasibility of tracking the development of AD before any of the symptoms take place by using plasma-based markers such as Aβ, Tau, and neurofilament light polypeptide (NFL) (24, 25). Through controlling and monitoring these markers could help provide additional tools that will be helpful in clinical practice for the early diagnosis of AD and for the tracking of the effectiveness of AD therapies with Aβ-targeting drugs (26). In a recent systematic review, a network of 250 miRNAs that has been associated with AD was cross-validated in the literature, this then revealed a group of 10 miRNAs that were able to diagnose the disease 20 years before the onset (27). One of the important aspects of AD biomarker development is the invasiveness of the test (27, 28). Current methods that are used are based on positron emission tomography (PET) imaging and also protein analysis in the CSF are very highly invasive and are relatively expensive (29, 30). Therefore, this would make large efforts in search for favourable and minimally invasive biomarkers of AD based on important sources for example blood, saliva, ocular fluids, and olfactory fluid (31, 32).

Biomarkers in AD

Imaging

As indicated above, three neuroimaging biomarkers for Alzheimer's disease are presently employed for research and, in some situations, to aid in clinical diagnosis (33, 34). Amyloid-specific imaging agents for positron emission tomography-computed tomography (PET/CT) can detect Aβ deposition 15 years prior to the onset of AD symptoms, whereas the next most sensitive metric, cerebral hypometabolism (FDG-PET), is detectable only 10 years prior to symptom onset (35-37). PET/CT is believed to predict reductions in even the most sensitive cognitive metrics, such as episodic memory, by ten years (38). An example of a biomarker for neurofibrillary tangles is increased cortical tau detected by PET imaging; impaired glucose metabolism detected by FDG-PET imaging and atrophy seen by structural MRI are biomarkers for neurodegeneration or neuronal damage (36, 39).

Cerebrospinal fluid biomarkers

Due to direct interaction between the brain and CSF, CSF reflects metabolic activities in the brain; hence, it has become a helpful fluid for diagnosing AD (40). CSF biomarkers are more desirable than plasma biomarkers due to their superior correlation with 11C-Pittsburgh compound B (PIB) PET imaging data and higher predictive value (41). Additionally, they increase the certainty of diagnosis, particularly in the prodromal phase or in unusual presentations (42). Currently, Aβ42, total tau (t-Tau), and p-Tau are the three canonical CSF biomarkers for diagnosing AD

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(43). Aβ42, t-Tau, and tau phosphorylated at threonine 181 are the most validated CSF biomarkers for AD (p-Tau181) (44). These biomarkers have consistently demonstrated a significant shift in AD and the early prodromal phase of the disease. In the cerebrospinal fluid (CSF) of AD patients, Aβ42 levels have repeatedly been lower, while tau and p-tau concentrations have risen (44). CSF tau and P-tau levels correspond with brain atrophy in Alzheimer's disease, whereas a drop of Aβ42 in CSF correlates with brain atrophy in non-demented individuals, indicating a potential preclinical stage (44). In addition, elevated CSF t-tau and p-tau predict the evolution of cognitive symptoms over a clinically relevant time frame (1–2 years) better than Aβ42 (45, 46). These core AD CSF biomarkers have been included in the diagnostic criteria for Alzheimer's disease due to their high diagnostic performance, as indicated previously (22). The interlaboratory and interassay variability of CSF indicators ranges from 20 to 30% (22). Standardization initiatives include the development of mass spectrometry (MS)-based reference measurement protocol (RMP) for CSF Aβ42 and certified reference materials (CRM) for the principal AD CSF biomarkers in an attempt to eliminate this variability. In addition to achieving precise measurements, novel tests designed using fully automated laboratory equipment have also been utilized (22). In addition, various A protein levels and ratios (tau/ Aβ42, Aβ42/ Aβ40, and Aβ42/ Aβ38) become aberrant when AD is present. For example, AD dementia and prodromal AD are decreased Aβ42/Aβ40 ratio (16, 47, 48).

The inherent heterogeneity in the progression of mounting plaque and tangle load over time between patients, as well as the presence of mixed pathologies and different comorbidities, are considered despite the promising CSF core biomarkers for the identification of presymptomatic AD and their ability to discriminate AD cases from healthy subjects. CSF levels of Aβ and Aβ imaging with PIB-PET do not correlate with cognitive deterioration (16). Therefore, proteins must be added to the CSF core biomarkers to improve diagnosis accuracy in longitudinal studies (6). Recently, it was claimed that novel biomarkers representing various features of pathology, such as CSF neurofilament light chain (NFL), neurogranin, and YKL-40 proteins, have achieved an advanced degree of clinical validation. According to a recent meta-analysis, the main CSF biomarkers of neurodegeneration (t-tau, p-tau, and Aβ42) and CSF NFL were substantially linked with AD, but NSE, VLP-1, HFABP, and YKL-40 were modestly associated with AD (6, 49). NFL, NSE, VLP-1, and H FABP are connected with neurodegeneration, while YKL-40 is linked to glial activation. In addition, neurogranin, a protein implicated in synaptic dysfunction and degeneration, was discovered in increased concentrations in the CSF of AD (6). Adding additional pathophysiological biomarker candidates that cover other critical AD pathways would probably make it easier to find, diagnose, and tell neurodegenerative diseases and dementias apart (6). It appears to be unique to AD and does not appear to change in most other neurodegenerative diseases (50, 51).

Blood-based biomarkers

Due to the invasive nature of lumbar puncture biomarker collection, their diagnostic use is limited. In this context, efforts are focused on identifying reliable blood biomarkers (52). Plasma and serum measurements are the gold standards in clinical settings since they are less intrusive and, therefore, easy to collect and evaluate (53, 54). Additionally, patients can be watched and evaluated for a prolonged time. However, blood biomarkers for AD have been more challenging to identify than CSF biomarkers (55). Plasma and serum data indicate a broad spectrum of abnormalities, not all of which are necessarily related to AD (56). Second, because only a tiny proportion of brain proteins enter the circulation, they must be evaluated in a matrix containing large numbers of plasma proteins, such as albumin and IgG, which poses a significant risk of analytical technique interference (56). In addition to dilution, brain proteins released into the blood may be degraded by proteases, metabolised in the liver, or removed by the kidneys, creating a separate and challenging-to-control variable (56). It is yet to be confirmed how well peripheral molecular alterations may accurately represent CNS dynamics on a broad scale, save for specific blood biomarkers such as plasma A and Tau, which have been directly studied in the same cohort (57, 58).

Aβ levels

Numerous reports have documented a substantial correlation between amyloid PET measures of plaque

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burden and a significant drop in Aβ42 in the CSF of AD patients (59). However, research on plasma Aβ42 as a biomarker has yielded disappointing and inconsistent results (13). Various investigations have demonstrated that plasma Aβ42 and Aβ40 levels can increase, decrease, or remain stable in AD patients compared to healthy controls. In addition, although prior longitudinal studies demonstrated that high plasma Aβ42 levels are a risk factor for AD development, others have linked low plasma Aβ42/Aβ40 ratios with an elevated risk for MCI and AD shortly (58). Thus, the widespread agreement is that this factor is neither sensitive nor specific for early diagnosis (58). Furthermore, there appears to be no correlation between CSF and plasma A levels, supporting the concept that plasma A levels reflect peripheral A production from other tissues rather than AD (60). Blood concentrations fluctuate over time and between individuals (61). In addition to binding to other proteins and getting immobilised, plasma Aβ expression is regulated by medications, and blood platelets contain considerable amounts of A, which regulates plasma Aβ levels directly (61).

In addition, analytical errors in ELISA or other traditional immunoassays might account for the weak disease association (58, 62). Several studies demonstrate that, due to their hydrophobicity, A peptides interact with several plasma matrix proteins, including albumin, 2-macroglobulin, and lipoproteins, among others (63). This might lead to epitope masking, preventing immunoassays from detecting up to 50% of these amyloid peptides (59). Consequently, this matrix effect may damage an individual's precision of Aβ peptide measurement. In 2011, Zetterberg's team developed a novel technique for quantifying Aβ42 in plasma based on the single-molecule array (Simoa) technology (64). Based on the immunocapture of the protein biomarker on magnetic beads, followed by the attachment of an enzyme-labelled detection antibody, this approach enables the exact measurement of Aβ 42 with high sensitivity and little matrix interference. The Swedish BioFINDER cohort study investigated this test and revealed that the ratio of plasma Aβ42/Aβ 40 in MCI and AD patients was considerably lower than in controls (54).

Also, the same authors have developed an immunoprecipitation (IP) mass spectrometry (MS) selected reaction monitoring method for measuring Aβ42 and Aβ40 in plasma (62, 65). Using this method, a brief pilot clinical trial comprising clinically diagnosed patients revealed only a trend toward reducing plasma Aβ42 and the Aβ42/ Aβ40 ratio in AD (62). A comparable IPMS approach revealed that the Aβ42 concentration and Aβ42/ Aβ40 ratio were significantly lower in amyloid PET-positive individuals than in PET-negative cases.

Additional MS-based studies suggest that a ratio of a particular APP fragment (APP669-711) to Aβ42 or Aβ40/ Aβ42 in plasma can identify Aβ-positive people with high sensitivity and specificity (52, 66). Specifically, plasma APP669-711/ Aβ42 and Aβ40/Aβ42 ratios were more remarkable in Aβ-positive individuals than in Aβ-negative individuals (52). These positive findings call for continued investigation in more extensive clinical cohorts to investigate plasma A as a diagnostic tool for amyloidosis of the brain and Alzheimer's disease (67).

Tau protein

Among all plasma and serum biomarkers, t-Tau is the only one that distinguishes AD patients from controls in most studies, indicating a slight rise in plasma Tau in AD patients but with too much overlap with controls to be diagnostically meaningful (22). Interestingly, longitudinal data have revealed significant relationships between plasma tau levels and future cognitive deterioration and increases in MRI-measured atrophy and FDG-PET-measured hypometabolism over the follow-up (68). Notably, tau protein in CSF has been identified as truncated fragments; hence, it is probable that the development of assays based on specific antibodies for these tau fragments may enhance performance (69). Alternately, the measurement of t-Tau or p-Tau in neuron-enriched exosome preparations may increase the performance of Tau as a blood biomarker. Nevertheless, this finding must be confirmed by other research (67, 70).

NFL protein

Numerous studies have demonstrated that AD patients have higher concentrations of NFL compared to age-matched controls, and other studies have demonstrated that blood NFL measurement could be used as a biomarker of neurodegeneration in the preclinical stage of AD (71). In 2016, the first Simoa

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technique for determining the axonal NFL protein concentration in blood samples was published. It is now the most replicated biomarker for AD in blood (63, 72). Intriguingly, while the decrease in the MCI group was less significant, plasma NFL was highest in MCI subjects with positive amyloid PET scans and predicted faster cognitive deterioration, a higher rate of future brain atrophy (measured by MRI), and hypometabolism as determined by FDG-PET (63, 64, 67). Furthermore, in familial AD research, NFL appears to be altered approximately a decade prior to the onset of symptoms, with levels corresponding to the projected year of symptom start and cognitive and MRI markers of disease progression (73). However, it is essential to note that the NFL is not a unique feature of AD. Elevated levels are observed in numerous neurodegenerative illnesses, including frontotemporal dementia, progressive supranuclear palsy, corticobasal syndrome, inflammatory conditions, and acute traumatic brain injury (67). Therefore, although the diagnostic specificity of NFL is poor, the semi-automated measurement of NFL in the blood allows for the collection of numerous samples to monitor illness progression and potentially therapy response (74). In the future, plasma NFL may be used as a simple, non-invasive, and inexpensive screening test during the initial clinical examination of individuals with cognitive problems, primarily to rule out neurodegeneration (24).

Addiction Diagnosis Utilizing Precision Medicine

AD is a disorder with a wide range of biomarker-derived "precision medicine"-oriented treatment techniques and/or data-driven pharmaceutical tactics that will considerably enhance the existing healthcare scenario with more effective therapy and the creation of disease-modifying medications for AD patients at any stage of the disease (75, 76). Since one of the pillars of "precision medicine" is biomarker-derived medical data, improvements in the acquisition, integration, interpretation, and bioinformatics aspects of clinical data, as well as the coordination and analysis of clinical, laboratory, molecular-genetic, neuroimaging, geriatric, and psychological data, as well as geriatric and psychological information and related healthcare resources, should significantly increase the accuracy of the diagnostic summary for the "prospective" patient (77). Multiple analytical molecular-genetic approaches, advancements in geriatric psychiatry and clinical evaluation, advancements in neuro-radiological labelling techniques and neuroimaging technologies, integrated diagnostic and predictive strategies and methodological improvements, and discoveries of the comprehensive pathophysiological profiles of complex multi-factor neurodegenerative diseases: (ii) have the potential to transform the diagnosis and treatment of neurodegenerative disorders; and (iii) less common clinical manifestations of AD are gradually becoming recognized, contributing to the growing abundance of AD biomarker information (17, 78).

Novel biomarkers and fluids: a look into the future

The hunt for non-invasive and easy-to-access biological systems, such as saliva, is undergoing active development (79). Recent measurements of Aβ42 or p-Tau in this fluid have yielded contradictory and inconclusive results (23). It should be noted that circadian fluctuations may significantly affect the content of saliva (80). Moreover, oral health or medication may influence the detection of biomarkers. In order to produce a reproducible result, it is vital to standardize the work methodology (3, 81).

In recent years, blood miRNAs have emerged as promising biomarkers for the early detection of AD (8). MicroRNAs are small non-coding molecules that function as epigenetic factors to regulate post-transcriptional gene expression by binding to complementary regions on target mRNAs (82). MicroRNAs are frequently contained in exosomes, microvesicles, or apoptotic bodies, which are structures capable of transporting other chemicals (83). Exosomes containing miRNAs can pass through the blood-brain barrier and mediate the cross-talk between blood, brain, and CSF (28, 84). Some of them have physiological and pathological functions, and several appear to be dysregulated in AD (28). APP, Tau, BACE, PSEN2, MAPK, and PSEN2 have binding sites in mRNAs that code for proteins that play a crucial role in AD (85). Under physiological conditions, exosomes can carry accumulated proteins (Aβ and Tau) to lysosomes or extracellular plasma for destruction. However, under diseased conditions, this clearance is interrupted. Although no conclusive results have been reported, a recent review suggests

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that has-miR-146a, has-miR-125b, and has-miR135a may be differentially expressed in the blood and CSF of AD patients compared to controls, patients with other neurological diseases, and even MCI patients (86, 87).

Conclusions

Classic AD diagnostic criteria are based on clinical evidence, but revised criteria are required to diagnose the illness in its earliest stages. Currently, it is believed that AD begins decades before clinical symptoms may be identified. If doctors could see changes in the body before they show up as symptoms, they could make a quick diagnosis and even change how they treat the disease.

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