Alzheimer’s disease: Newer biomarkers

ABSTRACT

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Fifty million people are affected with dementia worldwide with Alzheimer’s disease (AD) accounting for 70%–80% of these cases. In India alone, 4.1 million people suffered from dementia in 2015. To date, there are no definitive treatment options for AD and the overall treatment gap in India stands at 90%. Attempts have been made to define AD biologically. This has been made possible due to advances in the identification of biomarkers that indicate the neuropathological changes responsible for AD. Identification of these biomarkers has implications for disease staging, prognostication, and identifying drug targets. Here, we summarize the advances in the field of biomarkers in AD.

Keywords: Alzheimer’s disease, biomarkers, dementia, recent advances

Dementia is a syndrome of progressive impairment in multiple higher cortical functions in clear consciousness.[1,2] There are varied etiologies of dementia of which the neurodegenerative disorders comprise the vast majority. The most common of these is Alzheimer’s disease (AD) and either alone or in combination with other etiologies, it accounts for about 60%–80% of dementias.[3] Age is the single most important risk factor for dementia. The existing service gap for patients with dementia is 90%.[4] Apart from affecting the patient, the illness is associated with an increased burden of care and a huge economic impact.[5] This is likely to worsen with an increase in the number of cases due to the aging population. In 2011, National Institute on Aging and the Alzheimer’s Association proposed a clinical disease stage model. Three stages namely, preclinical, mild cognitive impairment, and dementia were identified.[6] Further, attempts have been made to define AD biologically based on biomarkers.[7] There are definitive benefits of identifying illness biomarkers. Biomarkers will help in arriving at a correct diagnosis and rule out other overlapping illness patterns. These biomarkers may have lesser implications for treatment at present, but they will be of use in understanding the underlying mechanism of disease and develop specific drugs in the future. Further, they will have a definitive role in assessing prognosis and measure the response to treatment.[8] In this short communication, we briefly touch upon the neurobiology of AD and highlight the recent advances in the field of biomarkers in AD.

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NEUROBIOLOGY OF ALZHEIMER’S DISEASE

Neuro-pathologically, AD is characterized by extracellular β-amyloid deposits, intracellular neurofibrillary tangles (NFT), dystrophic neuritis, and amyloid angiopathy. Amyloid cascade hypothesis and Tau hypothesis are commonly accepted pathological mechanisms of AD. The major processing pathway of amyloid precursor protein (APP) is nonamyloidogenic. It involves cleavage of APP by α-secretase occurring between Lys16 and Leu17 within the Aβ domain. This prevents the formation of Aβ peptides. During the process, soluble ectodomain of APP (sAPPα) is released and a 10-kDa C-terminal fragment (p3CT) remains within the membrane. Alternatively, proteolysis of APP via two-step process involving β- and γ-secretases leads to generation of Aβ. This is the amyloidogenic pathway. APP is first cleaved by the β-site APP cleaving enzyme (BACE1) which generates a membrane-bound soluble C-terminal fragment. Subsequent C-terminal fragment cleavage by the γ-secretase generates Aβ40 and Aβ42. Both these peptides are found in the amyloid plaque, with Aβ42 being directly neurotoxic. Furthermore, it has a greater tendency to aggregate.

The tau hypothesis relates to excessive or abnormal phosphorylation of tau which is a highly soluble microtubule-associated protein. This phosphorylation leads to the transformation of normal adult tau into paired helical filament-tau and NFTs. Through its isoforms and phosphorylation, tau protein interacts with tubulin to stabilize microtubule assembly. Other possible explanations are the inflammatory hypothesis, vascular hypothesis, and oxidative stress hypothesis. Factors in the amyloid pathway and tau pathway have been the targets of disease detection and development of disease-modifying agents for AD.

Biomarkers in AD can be studied broadly under two heads: (a) fluid biomarkers and (b) imaging biomarkers. Fluid biomarkers include amyloid-beta, tau, neuronal injury, synaptic dysfunction, and vascular dysregulation biomarkers. Molecular, structural, and functional imaging is included as imaging biomarkers.

AMYLOID BETA BIOMARKERS

Cerebrospinal fluid amyloid-beta 42
It has established a role in the early detection of AD. It has a predictive value in disease progression in cognitively unimpaired and those with mild cognitive impairment (MCI). However, the process is invasive and requires a lumbar puncture.

Blood Aβ and Aβ42/Aβ40 ratio
Early results were inconsistent, but with the development of ultrasensitive assays, it has shown promise as a less invasive means of detecting amyloid-beta pathology in blood. Levels correlate well with cerebrospinal fluid (CSF) levels and amyloid positron-emission tomography (PET) findings.

β-site APP-cleaving enzyme 1
Increased activity and protein levels are seen in AD patients compared to controls. BACE 1 has been shown to be a good progression marker in MCI patients.

TAU BIOMARKERS

Cerebrospinal fluid t-tau (total)
It is a marker of intensity of neuronal injury in AD. Hence, it has a clear diagnostic value for differentiating AD from normal aging.

Cerebrospinal fluid p-tau (phosphorylated)
It is a marker of tau deposition in AD and is more specific for AD compared to t-tau. CSF t-tau and p-tau levels are increased in AD compared with controls. CSF t-tau and p-tau levels correlate strongly with cognitive status compared to Aβ.

Serum or plasma t tau
Recent improvement in detection techniques has made it possible for tau proteins to be detected in blood. Increase in blood t-tau is seen in AD compared with controls. Further, it predicts cognitive decline and risk of dementia.

NEURONAL INJURY BIOMARKERS

Cerebrospinal fluid neurofilament light
It is an intermediate filament that is abundant in neuronal axons. It is widely accepted as a nonspecific biomarker of axonal injury.

Blood neurofilament light
Blood levels of NfL correlate with CSF levels. It has been shown to be associated with disease severity markers such as brain atrophy, glucose hypometabolism, and cognitive impairment. It has been proposed as a disease staging biomarker. Plasma/serum levels are higher in AD and MCI compared with controls.

Visinin-like protein 1
Visinin-like protein 1 (VILIP-1) is a Calcium sensor protein highly expressed in neurons. It is highly expressed in neurons. Intracellular expression is decreased in AD, especially in the entorhinal cortex. Levels have been found to correlate with...
t-tau and p-tau. It is increased in AD compared with patients with MCI and no cognitive dysfunction. Studies on blood VILIP-1 at present are limited.

**Synaptic dysfunction biomarkers**

Synaptic dysfunction and synapse loss are noted early in the pathogenesis of AD. It is closely associated with cognitive impairment. Main synaptic biomarkers that have shown promise can be classified as:

**Presynaptic (axonal)**

Synaptotagmin-1, synaptosomal-associated protein 25 (SNAP-25), and growth-associated protein 43 (GAP-43).

**Postsynaptic (dendritic)**

Neurogranin.

**Vascular dysregulation biomarkers**

Multiple risk factors are shared between cerebrovascular disease and AD. Vascular dysfunction has been proposed as one of the hypotheses for AD.

**Cerebrospinal fluid/serum albumin ratio**

It is a marker of blood–brain barrier integrity. A statistically significant increase is shown in AD compared to controls.

**Markers of pericyte breakdown**

CSF soluble platelet-derived growth factor receptor-β.

**Endothelial markers**

Vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 have been studied in AD. Levels in the CSF have been noted to be increased in preclinical, prodromal, and dementia stages of AD.

Inflammation: Misfolded and aggregated Aβ and tau proteins trigger an innate immune response. Existing inflammatory biomarkers results are inconsistent. Promising ones are soluble triggering receptors expressed on myeloid cells 2 (sTREM2), progranulin, and YKL-40 (chitinase-3-like protein 1).

**AMYLOID MOLECULAR IMAGING (POSITRON-EMISSION TOMOGRAPHY)**

Using amyloid-binding radiotracers can detect picomolar concentrations of amyloid. Amyloid load as measured by amyloid PET is highly correlated with disease progression. Increased amyloid uptake in MCI patients predicts progression to AD.

**Pittsburgh compound B tracer**

It is the radioactive analog of thioflavin T. Developed by the research team from the University of Pittsburgh led by geriatric psychiatrist William E. Klunk in the early 2000s. It is based on the 11-C radioisotope and due to its short half-life requires a cyclotron on site. Recently, dynamic 11-C Pittsburgh compound B PET has been used to demonstrate CSF clearance deficits associated with amyloid-β deposits.

New radiotracers based on the radionuclide fluorine 18 (18F) radioisotope do not require a cyclotron on site due to their longer half-life. They are:

- Florbetapir (FDA approved in 2012)
- Flutemetamol (can objectively evaluate amyloid positivity)

**TAU MOLECULAR IMAGING**

Tau accumulation in the medial temporal lobe is correlated with hippocampal atrophy, suggesting that tau deposits may be directly neurotoxic. Some researchers have found that compared to amyloid-beta deposits temporal lobe tau deposition was a better predictor of cognitive decline.

**18F-THK523**

This is a novel imaging radiotracer. It has a 410-fold increased affinity for tau in comparison to amyloid aggregates.

**11C-PBB3**

This radiotracer has minimal nonspecific interaction with white matter and other myelin-containing structures.

**Tauvid (flortaucipir F18)**

It can estimate the density and distribution of aggregated tau NFTs. It was FDA approved on May 28, 2020.

**MAGNETIC RESONANCE IMAGING**

**Magnetic resonance anatomical morphometry**

In comparison to CSF and PET biomarkers, hippocampal volume on MRI after correction for cranial volume has been found to be more sensitive for AD diagnosis. Cortical thinning has been found to be associated with cognitive decline.

**Functional magnetic resonance imaging**

Disruption in default mode network activity has been reported in AD patients compared to healthy controls. Diminished medial temporal lobe activation has been reported in AD patients compared to healthy controls.

**CONCLUSION**

Biomarkers of AD have the potential to aid in staging illness, prognostication. It will help in elucidating
mechanisms underlying disease and developing newer therapeutic agents. Significant advances have been made in the field of biomarkers in AD with identification of various fluid and imaging biomarkers. A huge number of publications in the field in the last one decade show that it remains an exciting field of research.

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REFERENCES

1. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva: World Health Organization; 1992.
2. Association AP. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). Washington: American Psychiatric Pub.; 2013.
3. Garre-Olmo J. Epidemiology of Alzheimer’s disease and other dementias. Rev Neurol 2018;68:377-88.
4. Nulkar A, Paralkar V, Juvekar S. Dementia in India – A call for action. J Glob Health Rep 2019;3:e2019078.
5. GBD 2016 Dementia Collaborators. Global, regional, and national burden of Alzheimer’s disease and other dementias, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:88-106.
6. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. Alzheimers Dement 2011;7:280-92.
7. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haierlein SB, et al. NIA-AA research framework: Toward a biological definition of Alzheimer’s disease. Alzheimers Dement 2018;14:535-62.
8. Mila-Alomà M, Suárez-Calvet M, Molinuevo JL. Latest advances in cerebrospinal fluid and blood biomarkers of Alzheimer’s disease. Ther Adv Neurol Disord 2019;12:1756286419888819.
9. Raskin J, Cummings J, Hardy J, Schuk K, Dean RA. Neurobiology of Alzheimer’s disease: integrated molecular, physiological, anatomical, biomarker, and cognitive dimensions. Curr Alzheimer Res 2015;12:712-22.
10. Mohandas E, Rajmohan V, Raghunath B. Neurobiology of Alzheimer’s disease. Indian J Psychiatry 2009;51:55-61.
11. Ferreira D, Rivero-Santana A, Perestelo-Pérez L, Westman E, Wahlund LO, Sarria A, et al. Improving CSF biomarkers’ performance for predicting progression from mild cognitive impairment to Alzheimer’s disease by considering different confounding factors: A meta-analysis. Front Aging Neurosci 2014;6:287.
12. Nakamura A, Kaneko N, Villenmaghe VL, Kato T, Doecke J, Doré V, et al. High performance plasma amyloid-β biomarkers for Alzheimer’s disease. Nature 2018;554:249-54.
13. Ewers M, Cheng X, Zhong Z, Nural HF, Walsh C, Meindl T, et al. Increased CSF-BACE1 activity associated with decreased hippocampus volume in Alzheimer’s disease. J Alzheimers Dis 2011;25:373-81.
14. Nelson PT, Alafuzoff I, Bigio EH, Bouras C, Braak H, Cairns NJ, et al. Correlation of Alzheimer disease neuropathologic changes with cognitive status: A review of the literature. J Neuropathol Exp Neurol 2012;71:362-81.
15. Mattsson N, Zetterberg H, Janelidze S, Insel PS, Andreasson U, Stomrud E, et al. Plasma tau in Alzheimer disease. Neurology 2016;87:1827-35.
16. Bos I, Vos S, Verhey F, Scheltens P, Teunissen C, Engelborghs S, et al. Cerebrospinal fluid biomarkers of neurodegeneration, synaptic integrity, and astroglial activation across the clinical Alzheimer’s disease spectrum. Alzheimers Dement 2019;15:644-54.
17. Mattsson N, Cullen NC, Andreasson U, Zetterberg H, Blennow K. Association between longitudinal plasma neurofilament light and neurodegeneration in patients with Alzheimer disease. JAMA Neurol 2019;76:791-9.
18. Mroczko B, Groblewska M, Zboch M, Muszyński P, Zajkowska A, Borawaska R, et al. Evaluation of visinin-like protein 1 concentrations in the cerebrospinal fluid of patients with mild cognitive impairment as a dynamic biomarker of Alzheimer’s disease. J Alzheimers Dis 2015;43:1031-7.
19. Tarawneh R, D’Angelo G, Mace Y, Xiong C, Carter D, Cairns NJ, et al. Visinin-like protein-1: Diagnostic and prognostic biomarker in Alzheimer disease. Ann Neurol 2011;70:274-85.
20. Bereczki E, Francis PT, Howlett D, Pereira JB, Höglund K, Bogstedt A, et al. Synthetic proteins predict cognitive decline in Alzheimer’s disease and Lewy body dementia. Alzheimers Dement 2016;12:1149-58.
21. Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer’s disease. Nat Rev Neurosci 2004;5:347-60.
22. Olsson B, Lautner R, Andreason U, Ohrfelt A, Portelius E, Bjørke M, et al. CSF and blood biomarkers for the diagnosis of Alzheimer’s disease: A systematic review and meta-analysis. Lancet Neurol 2016;15:673-84.
23. Montagne A, Barnes SR, Sweeney MD, Halliday MR, Sagare AP, Zhao Z, et al. Blood-brain barrier breakdown in the aging human hippocampus. Neuron 2015;85:296-302.
24. Janelidze S, Mattsson N, Stomrud E, Lindberg O, Palmqvist S, Zetterberg H, et al. CSF biomarkers of neuroinflammation and cerebrovascular dysfunction in early Alzheimer disease. Neurology 2018;91:e867-77.
25. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer’s disease. Lancet Neurol 2015;14:405-15.
26. Forsberg A, Engler H, Almkvist O, Blomqvist G, Hagman G, Wall A, et al. PET imaging of amyloid deposition in patients with mild cognitive impairment. Neurobiol Aging 2008;29:1456-65.
27. Rowley PA, Samsonov AA, Betthausser TJ, Pirasteh A, Johnson SC, Eisenmenger LB. Amyloid and Tau PET imaging of Alzheimer disease and other neurodegenerative conditions. Semin Ultrasound, CT MR. 2020; 41:572-583.
28. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, et al. Imaging brain amyloid in Alzheimer’s disease with Pittsburgh Compound-B. Ann Neurol 2004;55:306-19.
29. Schubert JJ, Veronesi M, Marchitelli L, Bodini B, Tonietti M, Stankoff B, et al. Dynamic 11C-PiB PET shows cerebrospinal fluid flow alterations in Alzheimer disease and multiple sclerosis. J Nucl Med 2019;60:1452-60.
30. Matsuda H, Ito K, Ishii K, Shimosegawa E, Okazawa H, Mishina M, et al. Quantitative evaluation of 18F-flutemetamol PET in patients with cognitive impairment and suspected Alzheimer’s disease: A multicenter study. Front Neurol 2020;11:578753.
31. Maruyama M, Shimada H, Suhara T, Shinotoh J, Ji B, Maeda J, et al. Imaging of tau pathology in a tauopathy mouse model and in Alzheimer patients compared to normal controls. Neuron 2013;79:1094-108.
32. Brier MR, Gordon B, Friedrichsen K, McCarthy J, Stern A, Christensen J, et al. Tau and Aβ imaging, CSF measures, and cognition in Alzheimer’s disease. Sci Transl Med 2016;8:338ra66.
33. Fodero-Tavoletti MT, Okamura N, Furumoto S, Mulligan RS, Connor AR, McLean CA, et al. 18F-THK523: A novel in vivo tau imaging ligand for Alzheimer’s disease. Brain 2011;134:1089-100.

34. FDA Approves Tauvid, First Drug to Help Image Certain Alzheimer’s Disease Signal. Healio. Available from: https://www.healio.com/news/primary-care/20200529/fda-approves-tauvid-first-drug-to-help-image-certain-alzheimers-disease-signal. [Last accessed on 2021 Mar 30].

35. Dickerson BC, Wolk DA, Alzheimer’s Disease Neuroimaging Initiative. MRI cortical thickness biomarker predicts AD-like CSF and cognitive decline in normal adults. Neurology 2012;78:84-90.

36. Kivistö J, Soininen H, Pihlajamaki M. Functional MRI in Alzheimer’s disease. In: Advanced Brain Neuroimaging Topics in Health and Disease Methods and Applications. IntechOpen; 2014. Available from: https://www.intechopen.com/chapters/46096. [Last accessed on 2021 Apr 05].