CONTEMPORARY DIAGNOSIS OF ALZHEIMER'S DISEASE – IMPORTANCE OF DIFFERENT BIOMARKERS

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Abstract

In preparation for the approval of new therapies for Alzheimer's disease (AD), a key step is the selection, validation and application of screening tests for disease detection and treatment monitoring. Biomarkers for AD have significantly advanced the field in several ways and hold promise for early diagnosis, determination of pathology, and measurement of response to treatment. The classic pathophysiological features of AD (beta-amyloid Aβ (A), tau (T) and neurodegeneration (N) can be determined in the cerebrospinal fluid (CSF), but their presence can also be demonstrated by different imaging techniques such as Positron Emission Tomography (PET), either with an amyloid marker or with tau-ligand as the gold standards of amyloid and tau pathology, in trials in clinical practice. Currently, there are no widely accepted blood tests for neuroinflammation, astrocytic, microglial activation in AB. However, both methods are either invasive and/or very expensive at the same time, so great efforts have been made to determine basic and more specific biomarkers in blood as a less invasive and more accessible procedure. In the primary health care setting, diagnostic algorithms from blood could already be sufficient to improve the accuracy of the clinical diagnosis of AB dementia and to positively influence the future treatment and care of people with cognitive problems. Additional studies are needed to evaluate the optimal combination of plasma biomarkers with other accessible and cost-effective procedures, such as, for example, MRI and cognitive tests, which are necessary for further development of predictive algorithms, which will be especially important in non-demented patients with cognitive problems.

Keywords: Alzheimer's disease, biomarkers, clinical diagnosis

Introduction

Alzheimer's disease (AD) is a insidious, slowly progressive neurodegenerative disease with a great social-economic impact. Unfortunately, there is currently no effective treatment that would cure or at least change the course of the disease. It is estimated that worldwide, around 50 million people have dementia, and most of these cases have got AD. In addition, a currently unknown number of individuals have presymptomatic pathology, representing an additional population of individuals who may benefit from treatment with novel disease-modifying therapies. A critical component of preparing for the approval of new treatments is the selection, validation, and application of screening tests for disease detection and treatment monitoring.

Initially, decades before clinical onset, accumulation of beta amyloid (Aβ) with a longer chain of 42 amino acids occurs in extracellular neuritic plaques in the brain[1]. Biomarker studies suggest that Aβ accumulation is accompanied by synaptic dysfunction. Further, there is increased phosphorylation and production of tau (phospho tau - F tau and total tau - T tau), an axonal protein that is highly expressed in cortical neurons, which binds to microtubules and leads to the production of intraneuronal neurofibrillary tangles[2]. The dysfunctional tau protein leads to neurodegeneration and eventually leads to the clinical manifestation of AB, with cognitive and behavioral symptoms that worsen as the disease progresses[3]. Such a scenario, the so-called amyloid hypothesis (cascade) has been largely confirmed in familial forms of the disease caused by monogenetic mutations in the genes encoding proteins related to beta-amyloid metabolism[4].

It seems that in sporadic AD (which is the most common form of the disease), a more complex interplay between Aβ aggregates, vascular changes, microglial and astrocytic activation, and other co-pathologies (eg. intracellular α-synuclein and TDP-43 inclusions) occur. Also, the influence of genetic polymorphism in the gene for apolipoprotein E [APOE]

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- subvariant APOE 4 which is only a susceptibility factor for the development of AB cannot be ignored. However, it should be noted that we do not know what exactly initiates the process of misfolding (conformation) of Aβ. It is unclear whether it is an increased production of Aβ and/or the clearance is not efficient enough, but a lot of experimental and observational data suggest that the accumulation of Aβ is not an innocent bystander and that it is toxic to synapses and neurons[5].

A biomarker is a physiological, biochemical or anatomical parameter that can be objectively measured as an indicator of normal biological and pathological processes or as a response to therapeutic intervention. In neurodegenerative diseases such as AD, biomarker development has been initiated using cerebrospinal fluid (CSF) as a matrix, since CSF, as opposed to peripheral blood, has the advantage of being in close proximity to the brain parenchyma, and with brain proteins secreted or released from neurons and from other types of brain cells in the extracellular space that communicate freely with the cerebrospinal fluid, which is available for sampling by lumbar puncture. Biomarkers that accurately reflect AD pathology are important for diagnosis in clinical practice, especially when disease-modifying therapies become available. The classic pathophysiological features of AD [beta-amyloid Aβ (A), tau (T) and an indicator of neurodegeneration (N)] could be easily determined in CSF. A recent meta-analysis showed consistent findings in CSF analyses from 231 publications including 15.699 patients with AD dementia and 13.018 controls with average levels as: a) 0.56 x reduction (95% CI 0.55–0.58) for Aβ 42; b) 2.54 x increase (95% CI 2.44–2.64) for T-tau; and c) 1.88 x increase (95% CI 1.79–1.97) for P-tau[2, 5]. Also, the presence of biomarkers can be shown by different imaging techniques such as Positron Emission Tomography (PET), either with amyloid marker or with tau-ligand as the gold standards of amyloid and tau pathology. However, both methods are either invasive and/or very expensive at the same time, therefore great efforts have been made to determine basic and more specific biomarkers in blood as a less invasive and more accessible procedure.

Biomarkers for AD have significantly advanced the field in several ways and enabling early diagnosis, determination of pathology, and measurement of response to treatment. However, identification of the best biomarkers, either alone or in combination, requires that biomarker modalities be examined mostly within the same individuals, and preferably in longitudinal cohort studies. The results of a large head-to-head comparison of biomarkers for Aβ and tau pathology, neuroinflammation, synaptic dysfunction and neurodegeneration in the Swedish BioFINDER[2] cohort were recently published. As predicted by previously published hypothetical models and the amyloid cascade hypothesis, the earliest changes in the BioFINDER study were found in Aβ42, followed by phosphorylated tau (P-tau) and total tau (T-tau), as markers of the Aβ response[3, 4]. Amyloid positivity change points were similar regardless whether CSF or plasma was used, but in both cases amyloid abnormalities in CSF and blood preceded the change in amyloid PET[5].

Neurodegeneration, indexed by hippocampal volume and neurofilament light chains (NfL) in the CSF and synaptic dysfunction along with neurogranin in the CSF, appear after positive amyloid PET findings. The inflammatory markers chitinase 3-like protein (YKL-40), a glycoprotein expressed in astrocytes and microglia, and the soluble form of TREM 2 (sTREM 2) are also being developed and tested. YKL-40 increases after the production of Aβ, P-tau and the development of neurodegeneration. Most likely, glial fibrillary acidic protein (GFAP) would follow a similar pattern, although we still lack longitudinal data for this marker[6]. Of particular note, both P-tau in CSF and in plasma had similar dynamic ranges[2], highlighting the potential for plasma P-tau to be used as a leading blood AD biomarker. sTREM 2 appears to peak early in the disease and decline later in the course of the AD[7].

Biomarkers for Aβ pathology

Extracellular deposition of Aβ into plaques, resulting from the cleavage of amyloid precursor protein (APP) by BACE1 and γ-secretase, is a key pathological feature of AD and it is the main pathogenic event in the disease[8]. In CSF, Aβ (Aβ42) 42 amino acid long chain prone to aggregation is characteristically reduced by approximately 50% of normal levels[9]. Aβ42 is a secreted by APP degradation and is normally mobilized from the brain interstitial fluid into the cerebrospinal fluid and blood9. In AD, it aggregates in the brain parenchyma, leading to decreased levels in the CSF. Diagnostic accuracy for Aβ pathology can be increased by using the ratio: concentration of Aβ42 (prone to aggregation) with soluble Aβ40 form (Aβ42/Aβ40). They are products of the same APP processing pathway, but Aβ40, unlike Aβ42, remains soluble in AD. The Aβ42/Aβ40 ratio in CSF, which explains the inter-individual differences is in 100% agreement with the finding on amyloid PET[10].

The amyloid PET method has passed a series of checks in the past 15 years: a) it has been validated in relation to neuropathology b) it has undergone extensive standardization regarding the quantification of Aβ pathology, c) in the definition of cut-off points for abnormality, d) it has appropriate criteria for use[11]. Amyloid PET is the most commonly used biomarker in current clinical trials and is likely to be the first choice for clinical use, especially in the US and Europe, when anti-amyloid therapy is approved. Despite all these advantages, we must not forget that the availability of PET scanners and cyclotron facilities varies from country to country.

Regarding imaging, three amyloid PET markers have been approved by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for in vivo imaging of amyloid plaques in patients with cognitive impairment clinically evaluable for AB: [18F] florbetapir (Amivid);

[18F] flutemetamol (Vizamil) and [18F] florbetaben (Neuracek) [11C]. PET is widely used in research, but due to the short half-life of carbon-11 (approximately 20 minutes), production requires an on-site cyclotron5. Reference methods and materials for the standardization of Aβ42 assays in CSF, as well as high-precision clinical chemistry assays on fully automated instruments, are in place which bodes well for the full implementation of these biomarkers in clinical laboratory practice with uniform reference limits for all centers worldwide[12]. In many European countries, CSF biomarkers are already used in clinical laboratory practice according to country-specific regulations.

Given that CSF sampling can be considered invasive, and on the other hand amyloid PET array with limited availability (and non-negligible radiation exposure) is expensive, a blood biomarker for cerebral Aβ pathology would be an important step towards accurate determination in clinical research of patients with cognitive problems. In contrast to earlier reports, recent findings suggest that plasma Aβ42 relative to Aβ40 (Aβ42/Aβ40) measured by immunoprecipitation mass spectrometry or ultra-sensitive enzyme-linked immunosorbent assays reflects cerebral Aβ pathology with relatively high accuracy[13]. The Aβ42/Aβ40 ratio, in patients with AD, is reduced by only 14-20% in plasma, compared to 50% decrease in CSF, which could be explained by the production of Aβ peptides in platelets and other non-cerebral tissues[14].

Biomarkers for tau pathology

Although tau inclusions in neurons or glial cells are also found in other neurodegenerative diseases[1, 2], the hyperphosphorylated form of the tau protein in neurofibrillary tangles is a key pathological feature of AD. T-tau and P-tau concentrations in the CSF reflect the pathophysiology associated with AD across neurodegenerative dementias. The increased levels of tau protein in the CSF, most likely are produced by the neurons, as a neuronal response to exposure to Aβ[15, 16]. Therefore, T -tau and P-tau in CSF can be considered as predictive markers for AD neurodegeneration type and clubbing formation, but not as direct markers of other non-Alzheimer diseases with tau pathology. Nowadays, fully automated tests are available for clinical use[13, 17].

Although ultrasensitive plasma T-tau assays can detect neuronal damage in acute brain disorders, such as stroke and traumatic brain injury[18, 19], they are relatively less accurate in AD, and the correlation with T-tau in CSF is poor. Contrary to this finding, it was recently shown that the test for P-tau 181 in plasma, which correlates with amyloid and tau PET, is a good predictor of AD typical brain pathology[2, 20]. It is interesting that P-tau 181 in plasma precedes the finding of positive amyloid PET, it can be useful for the detection of early disorders in tau-metabolism associated with Aβ pathology, as well as for determining the stage of the disease (although without anatomical precision)[21]. Recently, large validation studies show very similar results and confirm that plasma P-tau is a robust blood biomarker for AD pathology, and should be relatively easily standardized and implemented in daily clinical laboratory practice[22].

The main disadvantage of fluid biomarkers is the impossibility to use them to determine changes specific to the brain region, which limits the determination of the severity of the disease[23] and limits their use as markers of progression. Although far behind amyloid PET, the recently developed PET ligands to visualize, map and quantify tau pathology has provided new information on the temporal and spatial accumulation of tau in the brain[24].

In terms of accessibility and standardized use, tau imaging is still in its infancy compared to amyloid PET, but it could become a valuable clinical tool to assess the efficacy of amyloid, tau, or combination therapy. So far, the results obtained with PET imaging confirm the Braque model[23] of different stages of the progression of tau pathology in the brain in space and time AB[25] and the tau PET method has already been shown to be useful in clinical trials to detect the pharmacodynamic effects of disease-modifying drugs directed against Aβ (to monitor downstream tau changes) and tau pathology.

Biomarkers for neurodegeneration

Volumetric magnetic resonance imaging (vMR) and tau in the CSF are commonly used as biomarkers for neurodegeneration in AD[26]. Typical measures based on MR imaging include measures of whole brain atrophy, gray matter atrophy, regional atrophy (eg. medial temporal areas, hippocampus and hippocampal subfields)[27], as well as surface atrophy based on the thickness of the cerebral cortex. Advanced MR imaging sequences and subsequent software processing have also facilitated the characterization of cortical microstructural changes - which is a sensitive measure of neurodegeneration and precedes obvious loss cell[28]. Clinically, volumetric imaging is already used to monitor the progression of neurodegeneration and is available as part of commercial scanning packages.

T-tau in the CSF has been proposed as a strong candidate biomarker of neurodegeneration, but given that it reflects increased tau secretion from neurons affected by Aβ pathology rather than neuronal cell loss, it is a predictive but not a direct biomarker for neurodegeneration[21]. Recently, it has been shown that neurofilament light chains (NfL) emerged as a general biomarker for neuroaxonal degeneration and injury, regardless of cause[29]. The biomarker can be measured in both CSF and plasma (or serum), and virtually all findings from CSF have been replicated in blood using more sensitive assays[30]. The highest levels of NfL have been observed in frontotemporal, vascular and HIV-related dementias[31]. AD mutation carriers show a sudden change in NfL blood levels about a decade before the expected clinical

onset. The production of Nfl, probably marks the beginning of neurodegeneration, and the higher the increase, the faster the clinical progression of the disease. In sporadic AD, there is a clear association between Aβ and tau positivity with developing neurodegeneration and with increased plasma NfL concentrations. Most likely, due to the multitude of neurodegenerative changes that can lead to an increase in NfL in people over 70 years of age, these overlaps are greater in the sporadic than in the familial form of AB[32].

Biomarkers for synaptic dysfunction

Synaptic dysfunction appears to be an early event in AD, and synaptic loss is traditionally thought to correlate with cognitive impairment. In clinical practice fluoro-deoxyglucose (FDG) PET has long been used for differential diagnosis. Patients with AD dementia show a characteristic pattern of hypometabolism in the precuneus, posterior cingulum, parietal cortex, lateral temporal cortex, frontal cortex, and medial temporal lobe[33].

Hypometabolism probably reflects a combination of synaptic dysfunction, neuronal cell loss, and metabolic dysfunction in addition to affected astroglial glutamate transport[34]. Despite signal complexity, FDG PET remains an attractive biomarker, given its widespread clinical use for the differential diagnosis of AD, its likely sensitivity on synaptic dysfunction and its ability to detect abnormalities in the preclinical asymptomatic stage.

In biofluids, the most promising biomarker candidate for synaptic dysfunction in AB is the dendritic protein neurogranin (Ng). CSF Ng concentration is increased in AD and correlates with T-tau and P-tau concentrations, as well as with cognitive decline over time. CSF Ng concentration is normal or slightly reduced in neurodegenerative dementias without AD[34]. This finding suggests that it is not a general biomarker for synaptic loss, but to reflect Alzheimer's specific pathology and possibly Aβ alteration in its metabolism and secretion (similar to tau). The concentration of CSF Ng appears to correlate better with cognitive functioning compared to other biomarkers[35]. Ng can be measured in plasma but without correlation with CSF levels, possibly due to extra-cerebral protein production.

Biomarkers for glial activation and neuroinflammation

Neuroinflammation, as well as the activation of microglial cells and astrocytes, are the key features of neurodegenerative dementias, with the majority of research conducted in AD. Over the last decade, it has been debated whether neuroinflammation and astrogliosis are important drivers of neurodegeneration, or downstream effects of Aβ and tau accumulation. Variants in the gene for trigger receptor expressed on myeloid cells 2 (called TREM2), which is highly expressed in microglia, were found to increase the risk of late-onset AD by 2-4 fold, similar to what was observed in patients with a single copy APOE ε4[36]. This suggests that the innate immune system may be an active player in the AB process, potentially as a mediator of Aβ toxicity.

Numerous candidate markers related to inflammatory/astroglial activation in neurodegenerative dementias have been investigated, of which chitinase 3-like protein (YKL-40), a glycoprotein expressed in astrocytes and microglia, and the soluble form of TREM2 (sTREM2) have proven to be the most promising[36, 37]. Several cross-sectional as well as longitudinal follow-up studies in recent years have shown that CSF YKL-40 levels and sTREM2 are moderately increased in AD patients and correlate with CSF tau levels in Aβ-positive individuals. Data from a biomarker monitoring study in dominantly inherited Alzheimer's disease (DIAN) with familial carriers of AD mutations suggest that the concentration of CSF sTREM2 increases before the onset of the clinical manifestation of the disease, and immediately after CSF Aβ42 and T-tau in become positive.

There are currently no widely accepted blood tests for neuroinflammation, astrocytic, microglial activation. Recent data on plasma glial fibrillary acidic protein (GFAP), an intermediate filament protein selectively expressed in astrocytes in the central nervous system, show increased concentrations in patients with AD compared to cognitively normal controls[6].

Clinical interpretation of biomarker findings

As noted above, pathological findings associated with AD appear many years before the clinical onset of the disease. While positive Aβ and tau biomarkers suggest that a patient already has plaque and clubbing pathology, the challenge will be for clinicians to determine whether or not these pathologies explain the patient's symptoms. Age is another factor that is taken into account, especially with the "oldest old" people. Among cognitively intact older adults, knowledge of amyloid status may only partially influence lifetime risk of dementia. For example, a 60 to 65-year-old woman with cognitive impairment who is positive for amyloid has a lifetime risk of developing AD dementia of about 30%, while for an amyloid-positive 85-year-old woman, the lifetime risk is lower and is around 14%[38]. Similarly, the relationship between pathological brain lesions and clinical status appears to weaken with advanced age.

A postmortem evaluation of nearly 300 elderly subjects without neurological damage showed that approximately half of the subjects showed Aβ deposition, while some degree of tau pathology could be seen in almost all brains[39, 40]. Similarly, volumetric MRI changes typical of AB are commonly seen in cognitively healthy subjects over 80 years of age[40, 41].

Biomarkers in the new era of disease-modifying therapies

Results of recent clinical trials suggest that removal of cerebral Aβ plaques by antibody-based therapy may eventually challenge the formation of neurofibrillary tangles and slow cognitive decline in AB^{42}. Although it is still unclear whether this therapy will be approved by regulatory agencies in the USA or Europe (FDA and EMA), one thing is certain - the field of AD has been revived, and it is imperative that the health systems worldwide prepare for disease-modifying therapies against AD and biomarkers for it will be essential to this process as well as improved interpretation of biomarker results, taking into account the potential caveats discussed in this paper.

Conclusion

It is relatively easy to envision testing for Aβ and tau pathology using the plasma Aβ42/Aβ40 ratio and plasma P-tau as screening tools. While the difference in plasma Aβ42/Aβ40 ratio between Aβ-positive and negative individuals is quite modest (about 14-20% reduction), the increase in plasma P-tau concentration is about 3-fold, giving a very high diagnostic accuracy for AD (85-95%), suggesting that plasma P tau could serve as a screening test in blood and in primary care. Positive patients could then be referred to specialist memory clinics to be screened in more detail, undergo amyloid PET imaging where appropriate available and started treatment with anti-beta amyloid antibody therapy. Plasma P-tau (representing neuronal response to Aβ) and NfL levels (representing neurodegeneration) can be monitored during therapy (eg. at each antibody infusion or every 3 months), followed by amyloid PET scan yearly.

Repeated MRIs will initially be required to monitor possible amyloid-related adverse events (ARIAs), but in the future it is likely that increases in plasma NfL concentrations could replace MRIs for the detection of clinically relevant ARIAs. The patient would then be treated until the amyloid PET was negative or the plasma P-tau concentration normalized. After treatment, the patient can be monitored with annual plasma P-tau measurements, to assess the need for additional therapy. As additional therapies will be developed, for example, microglia modulators or treatments that improve synaptic function, biomarkers associated with these processes are expected to facilitate monitoring of therapy efficacy.

Blood and CSF biomarkers provide an attractive option for screening and early detection of AD and monitoring treatment efficacy, given the potential barriers that may impede access to the disease modifying therapy, and the need to expand treatment options beyond specialized centers. This approach could be a testable scenario for how future clinical trials could be designed, and how treatments proven to be successful could be implemented in everyday clinical practice with the support of biomarkers.

References

1. DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. Mol Neurodegener. 2019;14:32.
2. Palmqvist S, Insel PS, Stomrud E, Janelidze S, Zetterberg H, Brix B, et al. Cerebrospinal fluid and plasma biomarker trajectories with increasing amyloid deposition in Alzheimer's disease. EMBO Mol Med. 2019;11:e11170.
3. Jack CR Jr., Holtzman DM. Biomarker modeling of Alzheimer's disease. Neuron. 2013;80:1347–58.
4. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. Science. 1992;256:184–5.
5. Cohen AD, Landau SM, Snitz BE, Klunk WE, Blennow K, Zetterberg H. Fluid and PET biomarkers for amyloid pathology in Alzheimer's disease. Mol Cell Neurosci . 2019;97:3–17.

6. Bogoslovsky T, Wilson D, Chen Y, Hanlon D, Gill J, Jeromin A, et al. Increases of Plasma Levels of Glial Fibrillary Acidic Protein, Tau, and Amyloid beta up to 90 Days after Traumatic Brain Injury. J Neurotrauma. 2017;34:66–73.
7. Suarez-Calvet M, Kleinberger G, Araque Caballero MA, Brendel M, Rominger A, Alcolea D, et al. sTREM2 cerebrospinal fluid levels are a potential biomarker for microglia activity in early-stage Alzheimer's disease and associate with neuronal injury markers. EMBO Mol Med. 2016;8:466–76.
8. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med. 2016;8:595–608.
9. Olsson B, Lautner R, Andreasson U, Ohrfelt A, Portelius E, Bjerke 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.
10. Hansson O, Lehmann S, Otto M, Zetterberg H, Lewczuk P. Advantages and disadvantages of the use of the CSF Amyloid beta (Abeta) 42/40 ratio in the diagnosis of Alzheimer's Disease. Alzheimers Res Ther. 2019;11:34.
11. Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, et al. Update on appropriate use criteria for amyloid PET imaging: dementia experts, mild cognitive impairment, and education. Amyloid Imaging Task Force of the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging. Alzheimers Dement. 2013;9:e106–9.
12. Leitao MJ, Silva-Spinola A, Santana I, Olmedo V, Nadal A, Le Bastard N, et al. Clinical validation of the Lumipulse G cerebrospinal fluid assays for routine diagnosis of Alzheimer's disease. Alzheimers Res Ther. 2019;11:91.
13. Palmqvist S, Janelidze S, Stomrud E, Zetterberg H, Karl J, Zink K, et al. Performance of Fully Automated Plasma Assays as Screening Tests for Alzheimer Disease-Related beta-Amyloid Status. JAMA Neurol. 2019 Sep 1;76(9):1060-1069.
14. Schindler SE, Bollinger JG, Ovod V, Mawuenyega KG, Li Y, Gordon BA, et al. High-precision plasma beta-amyloid 42/40 predicts curr ent and future brain amyloidosis. Neurology. 2019;93:e1647–e59.
15. Skillback T, Farahmand BY, Rosen C, Mattsson N, Nagga K, Kilander L, et al. Cerebrospinal fluid tau and amyloid-beta(1-42) in patients with dementia. Brain. 2015;138:2716–31.
16. Sato C, Barthelemy NR, Mawuenyega KG, Patterson BW, Gordon BA, Jockel-Balsarotti J, et al. Tau Kinetics in Neurons and the Human Central Nervous System. Neuron. 2018;98:861–4.
17. Blennow K, Shaw LM, Stomrud E, Mattsson N, Toledo JB, Buck K, et al. Predicting clinical decline and conversion to Alzheimer's disease or dementia using novel Elecsys Abeta(1-42), pTau and tTau CSF immunoassays. Sci Rep. 2019;9:19024.
18. De Vos A, Bjerke M, Brouns R, De Roeck N, Jacobs D, Van den Abbeele L, et al. Neurogranin and tau in cerebrospinal fluid and plasma of patients with acute ischemic stroke. BMC Neurol. 2017;17:170.
19. Zetterberg H Review: Tau in biofluids - relation to pathology, imaging and clinical features. Neuropathol Appl Neurobiol. 2017;43:194–9.
20. Mielke MM, Hagen CE, Xu J, Chai X, Vemuri P, Lowe VJ, et al. Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography. Alzheimers Dement. 2018;14:989–97.
21. Pereira JB, Westman E, Hansson O, Alzheimer's Disease Neuroimaging I. Association between cerebrospinal fluid and plasma neurodegeneration biomarkers with brain atrophy in Alzheimer's disease. Neurobiol Aging. 2017;58:14–29.
22. Thijssen EH, La Joie R, Wolf A, Strom A, Wang P, Iaccarino L, et al. Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration. Nat Med. 2020 Mar;26(3):387-397.
23. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 1991;82:239–59.
24. Janelidze S, Mattsson N, Palmqvist S, Insel P, Smith R, Eichenlaub U, et al. Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. Nat Med. 2020 Mar;26(3):379-386.
25. Scholl M, Maass A, Mattsson N, Ashton NJ, Blennow K, Zetterberg H, et al. Biomarkers for tau pathology. Mol Cell Neurosci. 2019;97:18–33.
26. Frisoni GB, Fox NC, Jack CR Jr., Scheltens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. Nat Rev Neurol. 2010;6:67–77.
27. Dickerson BC, Stoub TR, Shah RC, Sperling RA, Killiany RJ, Albert MS, et al. Alzheimer- signature MRI biomarker predicts AD dementia in cognitively normal adults. Neurology. 2011;76:1395–402.
28. Vogt NM, Hunt JF, Adluru N, Dean DC, Johnson SC, Asthana S, et al. Cortical Microstructural Alterations in Mild Cognitive Impairment and Alzheimer's Disease Cereb Cortex. 2020 May 14;30(5):2948-2960.
29. Khalil M, Teunissen CE, Otto M, Piehl F, Sormani MP, Gattringer T, et al. Neurofilaments as biomarkers in neurological disorders. Nat Rev Neurol. 2018;14:577–89.
30. Gaetani L, Blennow K, Calabresi P, Di Filippo M, Parnetti L, Zetterberg H. Neurofilament light chain as a biomarker in neurological disorders. J Neurol Neurosurg Psychiatry. 2019;90:870–81.
31. Bridel C, van Wieringen WN, Zetterberg H, Tijms BM, Teunissen CE, and the NFLG, et al. Diagnostic Value of Cerebrospinal Fluid Neurofilament Light Protein in Neurology: A Systematic Review and Meta-analysis. JAMA Neurol. 2019 Sep 1;76(9):1035-1048.
32. 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.
33. Alexander GE, Chen K, Pietrini P, Rapoport SI, Reiman EM. Longitudinal PET Evaluation of Cerebral Metabolic Decline in Dementia: A Potential Outcome Measure in Alzheimer's Disease Treatment Studies. Am J Psychiatry. 2002;159:738–45.
34. Portelius E, Olsson B, Hoglund K, Cullen NC, Kvartsberg H, Andreasson U, et al. Cerebrospinal fluid neurogranin concentration in neurodegeneration: relation to clinical phenotypes and neuropathology. Acta Neuropathol. 2018;136:363–76.
35. Casaletto KB, Elahi FM, Bettcher BM, Neuhaus J, Bendlin BB, Asthana S, et al. Neurogranin, a synaptic protein, is associated with memory independent of Alzheimer biomarkers. Neurology. 2017;89:1782–8.
36. Gratuze M, Leyns CEG, Holtzman DM. New insights into the role of TREM2 in Alzheimer's disease. Mol Neurodegener. 2018;13:66.
37. Molinuevo JL, Ayton S, Batrla R, Bednar MM, Bittner T, Cummings J, et al. Current state of Alzheimer's fluid biomarkers. Acta Neuropathol. 2018;136:821–53.
38. Brookmeyer R, Abdalla N. Estimation of lifetime risks of Alzheimer's disease dementia using biomarkers for preclinical disease. Alzheimers Dement. 2018;14:981–8.
39. Elobeid A, Libard S, Leino M, Popova SN, Alafuzoff I. Altered Proteins in the Aging Brain. J Neuropathol Exp Neurol. 2016;75:316–25.
40. Mattsson N, Rosen E, Hansson O, Andreasen N, Parnetti L, Jonsson M, et al. Age and diagnostic performance of Alzheimer disease CSF biomarkers. Neurology. 2012;78:468–76.
41. Tang Y, Whitman GT, Lopez I, Baloh RW. Brain volume changes on longitudinal magnetic resonance imaging in normal older people. J Neuroimaging. 2001;11:393–400.
42. Haeberlein SB, von Hehn C, Tian Y, Chalkias S, Muralidharan KK, Chen T, et al. Topline results from phase 3 aducanumab studies Clinical Trials on Alzheimer's Disease. 2019.

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