Chapter 11
Spinal fluid

Pedro Rosa-Neto, Eduardo Zimmer

Key points

- Lumbar puncture (cerebrospinal fluid or CSF) is a safe and acceptable procedure towards a specific diagnosis in people with dementia of uncertain aetiology.

- Cerebrospinal fluid analysis biomarkers constitute an affordable alternative to imaging biomarkers, with excellent diagnostic properties.

- There is a need for cerebrospinal fluid biomarkers specific for dementias of causes other than Alzheimer's disease.

- Accessibility to cerebrospinal fluid analytical infrastructure remains unavailable in the vast majority of low- and middle-income countries.

This is a chapter of the *World Alzheimer Report 2021, Journey to a Diagnosis of Dementia* which can be accessed in full at: https://www.alzint.org/resource/world-alzheimer-report-2021/

General background

Cerebrospinal fluid (CSF) is a clear fluid that protects and supplies nutrients and clears metabolic waste from the brain and spinal cord. Every day, the brain produces nearly half a litre of cerebrospinal fluid, which carries proteins associated with neurodegenerative conditions. The CSF obtained via lumbar puncture is a safe and cost-efficient way to identify the presence of a pathological process in the brain.

> **The CSF obtained via lumbar puncture is a safe and cost-efficient way to identify the presence of a pathological process in the brain.**

Cerebrospinal fluid profile provides information regarding the underlying cause of dementia

In the field of dementia, biomarkers are defined as objective measures of biological or pathogenic processes obtained in living individuals (1). Measures of amyloid or neurofibrillary tangles are biomarkers of brain protein aggregation and reflect the core brain pathology underlying Alzheimer's disease. Unfortunately, apart from Alzheimer's disease, there are no biomarkers specific for other neurodegenerative conditions. Biomarkers of neurodegeneration designate tests (that is, structural MRI, PET-FDG, Nfl and total-tau in the CSF) assess brain damage secondary to Alzheimer's disease or other neurodegenerative dementias. Brain atrophy, reduction of metabolism, release of tau protein in the CSF are measures of brain damage present in all dementias (2). Biomarkers of neurodegeneration can be obtained using MRI, PET, cerebrospinal fluid or blood. Regarding their origin, they are designated as imaging or fluid biomarkers. It is expected that researchers will develop biomarkers able to identify protein aggregates such as alpha-synuclein, 3-R or 4R tau, TDP-43.

The cerebrospinal fluid is an optimal source for Alzheimer's disease biomarkers due to its direct contact with the brain's extracellular space. This physical contiguity between the brain and CSF is advantageous to obtain information regarding abnormal brain processes (3).

As dementia can be caused by various diseases, the goal of cerebrospinal fluid biomarkers in clinical practice is to diagnose Alzheimer's disease in people with dementia

(4). Indeed, one might claim that cerebrospinal fluid biomarkers have an advantage over their PET counterparts by providing a measure of brain amyloid pathology (Aβ42), and t-tau (neurodegeneration), and p-tau (neurofibrillary tangles) in a single test. In fact, cerebrospinal fluid information is sufficient to meet the requirements for the 2018 operational definitions of Alzheimer's disease.

Fluid biomarkers analysis improves the diagnostic of the underlying cause of dementia using a more affordable technology as compared to PET scans. The role of fluid biomarkers in patient care is an evolving field in the face of recent developments of biomarkers for other neurodegenerative conditions (5).

Although cerebrospinal fluid biomarkers are well-established clinic diagnostic tests in some European countries, they are not routine clinical practice elsewhere. The major obstacle impeding CSF dissemination is the availability of an appropriated laboratory infrastructure for analysis.

The most studied biomarkers for dementia are the monomeric form of amyloid beta 42 (Aβ42), the total tau (t-tau), and the tau phosphorylated at threonine 181 (p-tau-181) (see Table 1).

Amyloid isoforms

Aβ42 is one of the most abundant amyloid species in the CSF. It is produced during normal cell metabolism and is secreted into the extracellular space. As Aβ42 is retained in amyloid plaques in the brain of people with Alzheimer's disease, CSF Aβ42 in Alzheimer's disease is decreased to approximately 50% of control levels. Although methodology to quantify Aβ species is mature, cerebrospinal fluid handling from collection to the analysis may be complex due to the Aβ42 physicochemical properties. The ratio between Aβ42/40 has been proposed as a robust measure of amyloidosis, however its use remain restricted to selective clinical centres (3,6).

Phosphorylated tau isoforms

Tau is a neuronal protein part of the skeleton of the brain cells with a large number of phosphorylation sites. Hyperphosphorylation of tau constitutes an important molecular abnormality of Alzheimer's disease. In fact, neurofibrillary tangles are composed by the aggregation of hyperphosphorylated tau. P-tau CSF analysis targets specific to certain phosphorylation sites, namely the 181 (p-tau181) or 217 (p-tau-217) were recently recognised for their excellent diagnostic performance of Alzheimer's disease. Studies using these assays have consistently revealed a robust increase in CSF P-tau in Alzheimer's disease but not in t=other dementia conditions. All phospho-tau isoforms are considered as core biomarkers of Alzheimer's disease (7–9).

Total tau protein

Total tau measured in the CSF belongs to a pool of cytoskeleton proteins secreted to the extracellular space. In the CSF, total tau provides a metric of brain integrity, independent of specific neuronal insult. Cerebrospinal fluid t-tau in Alzheimer's disease might reach 300% of control levels. Total tau is considered a biomarker of neurodegeneration (10).

Several consensus recommendations have been published to provide guidance in the utilisation of cerebrospinal fluid in dementia or predementia cases. In summary, these biomarker tests seem particularly useful in the diagnostic workup of individuals of atypical cases, early-onset dementia and rapid progressive cases (11–13).

Limitations regarding the use of cerebrospinal fluid in dementia diagnosis

The dissemination of cerebrospinal fluid biomarkers is hampered by several factors. First, lumbar punctures remain a complex procedure to be conducted as routine in primary care. Second, handling of CSF samples requires some degree of expertise. Third, analytical infrastructure remains confined at expert centres. Fourth, the absence of cerebrospinal fluid biomarkers for diagnosis of other dementia diseases constitutes an important diagnostic limitation.

Table 1. Clinically relevant cerebrospinal fluid biomarkers for Alzheimer's disease

Pathophysiology	Biomarker	Key References
Amyloid pathology (biomarker of)	AB1–42 (AB 42/40 ratio)	
Tau pathology (core Alzheimer's disease biomarker)	p-tau-181, p-tau-217	(14) (7) (8) (6)
Neurodegeneration (not specific)	t-tau, NfL	

Survey results

The 1,111 multidisciplinary clinicians who responded to the survey revealed that only 35% of clinicians use lumbar punctures to assist in the diagnosis of dementia in selected cases based on national practice guidelines, while 5% of clinicians do this in all patients (Chart 1). These lumbar punctures are mostly performed by neurologists (Chart 2). These responses support the idea that although lumbar punctures constitute an acceptable method for assessing people with dementia (Chapter 11), they are currently underutilised.

Lumbar puncture and cerebrospinal fluid seem to offer an affordable alternative for imaging biomarkers. However, there are limitations regarding the accessibility of CSF infrastructure for the analysis of cerebrospinal fluid.
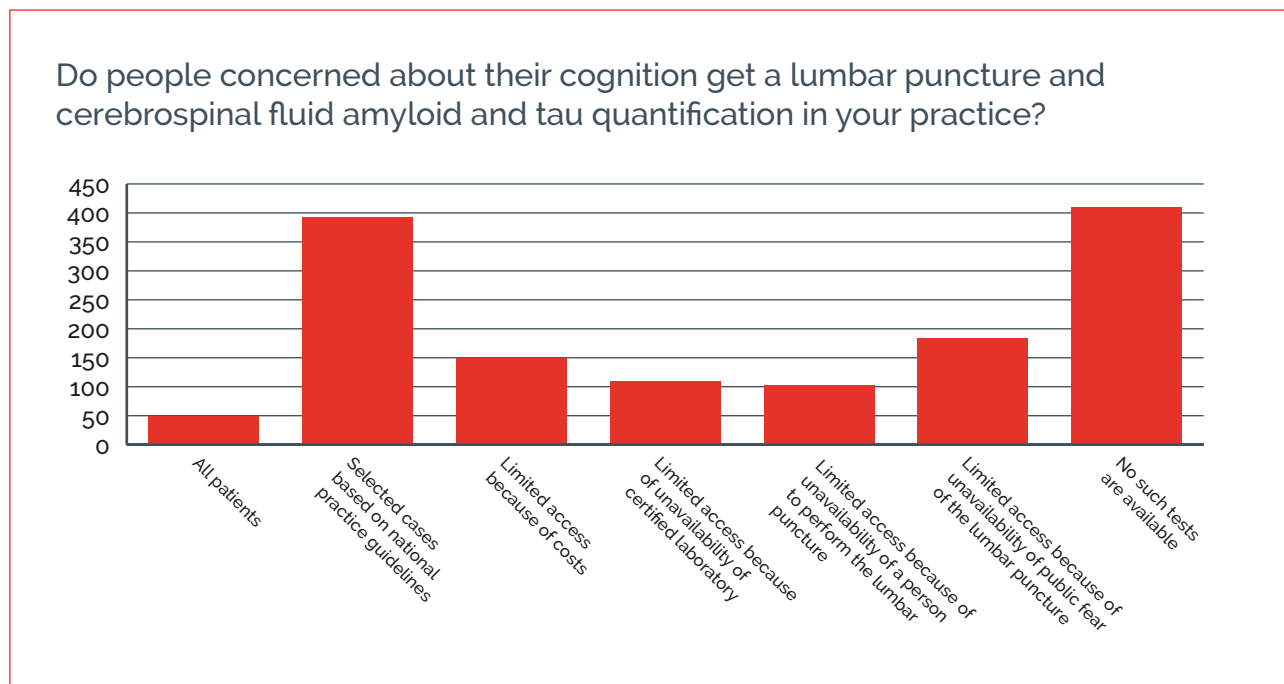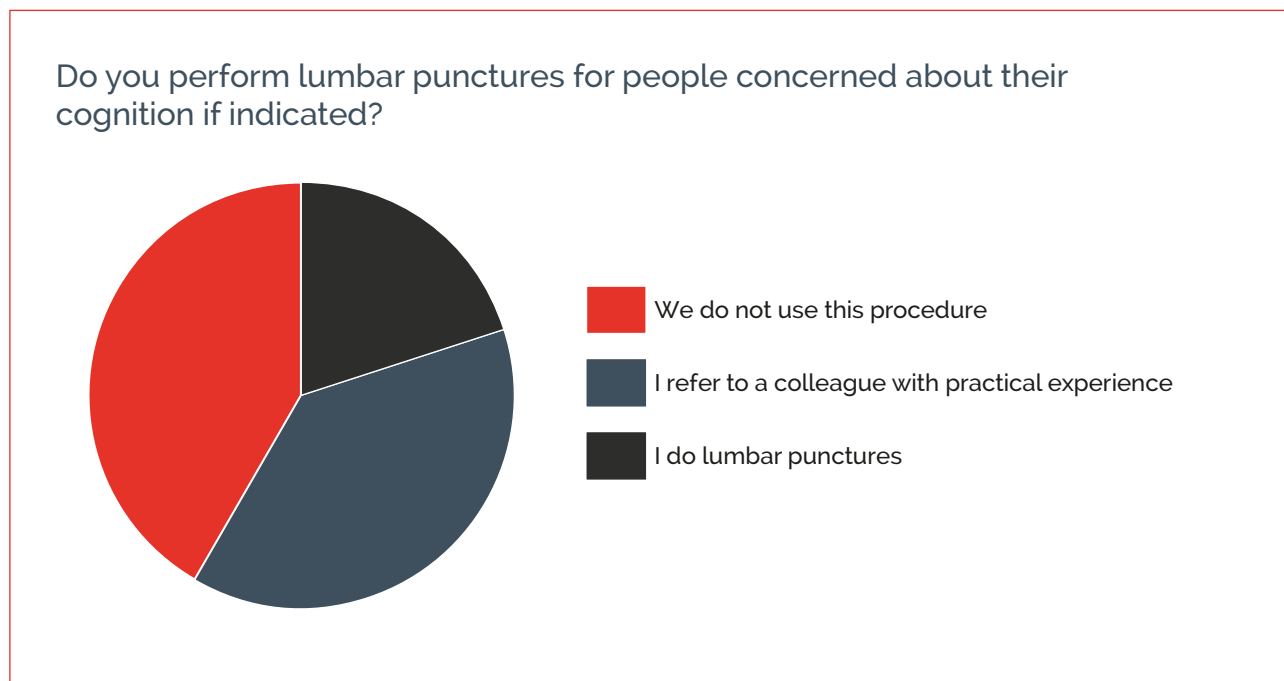

Chart 1. Clinician responses.

Chart 2. Clinician responses.

Expert essay

How to reassure people in need of a lumbar puncture

Paolo Vitali

McGill University Research Centre for Studies in Aging, CANADA

Lumbar puncture is a unique medical procedure to collect samples of cerebrospinal fluid (CSF) surrounding brain and spinal cord. It represents a relatively non-invasive way to gain direct access to the central nervous system, compared to other more aggressive surgical techniques such as brain biopsy or external ventricular drain. Given its proximity to the central nervous system structures, CSF analysis provides vital information about pathophysiological processes underlying neurological disorders, such as infectious, inflammatory, autoimmune, and neoplastic diseases.

There is no denying that the prospect of a lumbar puncture procedure is very stressful for most people. One way to mitigate the anxiety related to the technique is to keep the individual informed every step of the way throughout the procedure, explaining in simple terms why and how the lumbar puncture is performed, detailing whether there is any associated discomfort or risk, and how to go about minimising the possible minor side effects.

Below is a review of the important features of a lumbar puncture, all with the aim to reassure people who will undergo the procedure.

What to expect?

The procedure lasts approximately 15 minutes and basically consists of inserting a small atraumatic needle into the lower back, similar to the epidural procedure for pregnant women during labour. Before the lumbar puncture itself, people are asked to lie down comfortably on their side or sit with their back arched. The back is then cleansed with antiseptics to prevent infections. Subsequently, a local anaesthesia, (like a dental anaesthesia) is provided. The anaesthesia will numb most of the discomfort experienced from the insertion of the spinal needle. During the lumbar puncture, a needle will be inserted, under aseptic conditions, between two of the bones in the back into a fluid-filled space. The needle enters a space below the actual spinal cord. The lower back is generally considered the safest site to perform a lumbar puncture. Once the needle attains the fluid space, the spinal fluid will

be removed for testing. After the lumbar puncture, the person will be asked to drink water or juice and rest in a bed for at least one hour. The amount of spinal fluid removed is naturally replaced by the body after approximately one hour. People are generally invited to avoid driving after a lumbar puncture. The next day, a follow-up call is made to verify that everything is fine and answer questions.

Why perform a lumbar puncture in patients with memory changes?

In memory clinics, lumbar puncture is largely performed by trained physicians to investigate in cognitively impaired patients the presence of abnormal proteins in the CSF, which are generally associated with underlying neurodegenerative conditions. Detection of abnormal values of amyloid beta, tau and phospho-tau in CSF can help diagnose Alzheimer's disease. In Canada, CSF analysis is not recommended routinely, but it can be considered in symptomatic patients with diagnostic uncertainty and onset at an early age (<65) to rule out Alzheimer's disease pathophysiology. CSF analysis can also be considered in patients with atypical cognitive deficits such as predominance of language, visuospatial, dysexecutive, or behavioural features to rule out Alzheimer's disease pathophysiology (2). A CSF-based diagnosis will eliminate diagnostic incertitude and help people receive more adequate treatments and appropriate referral to clinical trials if available.

Will it be painful?

Contrary to what is commonly believed, due to the anaesthetic most people do not feel any discomfort during a lumbar puncture, except for some pressure in the back. In most memory clinics, especially where research lumbar punctures are performed, physicians are required to complete a lumbar puncture certificate to guarantee that the standard operational procedures respected. Complying with evidence-based guidelines contributes to reduced discomfort and complication rates. It has been proven that the use of atraumatic (small) needles with an introducer, not more than four lumbar puncture attempts, passive withdrawal of

CSF (instead of active withdrawal using a syringe), collection of up to 30 mL of CSF, and the lateral recumbent position minimise complaints and complications (3).

Which are the risks?

Lumbar puncture is considered a safe procedure. Post-lumbar puncture complaints are generally mild and severe complications are extremely rare (< 0.01%) (4). Per procedure, nerve root irritation by the needle – occasioning intermittent electric shocks down in one leg – is relatively common, but not dangerous nor associated to any complication. After the procedure, lower back pain may be experienced, which is essentially related to the number of attempts and failures. For the experienced physician, this amount is low. Post lumbar puncture headache is the most frequent complication and occurs in 9% of cases (4). Classically, this happens over the subsequent three days when sitting or standing and subsides when lying down. To prevent this, people are asked to rest at for least one hour after the LP and drink plenty of water (or coffee, which stimulates CSF production). Over the next 24 hours, people are also instructed to refrain from strenuous physical activities. If typical post lumbar puncture headache symptoms arise, the individual is advised to lie down and continue to stay well hydrated. Simple analgesics can help. If the pain persists for a couple of days, a simple procedure, called epidural blood patch, is performed at the emergency department and provides immediate relief. This is done by withdrawing an individual's own blood and injecting it back into the lumbar puncture site where there may be some leaking spinal fluid. This relieves the pressure and seals the leak. Generally, only 0.3% of people need a blood patch procedure. (4).

It should be noted that individuals under the age of 40 typically have higher instances of post lumbar puncture headaches, while conversely, those experiencing cognitive complaints seem to have a protective barrier. (4).

References

1. Rosa-Neto P, Gauthier S. Standard operational procedures (SOP) to perform Cerebral Spinal Fluid Sampling at the Douglas Hospital n.d.

2. Ismail Z, Black SE, Camicioli R, Chertkow H, Herrmann N, Laforce R, et al. Recommendations of the 5th Canadian Consensus Conference on the diagnosis and treatment of dementia. Alzheimer's Dement 2020;16:1182–95. https://doi.org/10.1002/alz.12105.

3. Engelborghs S, Niemantsverdriet E, Struyfs H, Blennow K, Brouns R, Comabella M, et al. Consensus guidelines for lumbar puncture in patients with neurological diseases. Alzheimer's Dement Diagnosis, Assess Dis Monit 2017;8:111–26. https://doi.org/10.1016/j.dadm.2017.04.007.

4. Duits FH, Martinez-Lage P, Paquet C, Engelborghs S, Lleó A, Hausner L, et al. Performance and complications of lumbar puncture in memory clinics: Results of the multicenter lumbar puncture feasibility study. Alzheimer's Dement 2016;12:154–63. https://doi.org/10.1016/j.jalz.2015.08.003.

5. Amorim JA, Gomes De Barros M V., Valença MM. Post-dural (post-lumbar) puncture headache: Risk factors and clinical features. Cephalalgia 2012;32:916–23. https://doi.org/10.1177/0333102412453951.

Expert essay

CSF biomarkers for Alzheimer's disease

Henrik Zetterberg, Kaj Blennow

Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, SWEDEN

The development of Alzheimer's disease fluid biomarkers started with using cerebrospinal fluid (CSF) as the matrix, which was logical based on the proximity of CSF to the brain, and the secretion (at that time called 'shedding') of brain proteins from neurons and other cell types to the extracellular space, which is continuous with the CSF. CSF can easily be collected by lumbar puncture (1).

Based on the knowledge of Alzheimer's disease pathophysiology, methods for the quantification of CSF levels of 'total' tau (T-tau), phosphorylated tau (P-tau) and amyloid b ($A\beta42$ and $A\beta42/40$ ratio) were developed. These proteins are often referred to as the 'core' Alzheimer's disease CSF biomarkers. The typical changes in Alzheimer's disease, namely the increased CSF levels of T-tau (reflecting neurodegeneration) and P-tau (a marker for tangles and tau pathology) together with decreased $A\beta42$ and $A\beta42/40$ ratio (reflecting brain amyloidosis and plaques), are often called the 'Alzheimer CSF profile'.

A very large number of clinical studies consistently show that these core Alzheimer's disease CSF biomarkers reflect key parts of Alzheimer's disease pathophysiology and have high diagnostic value, also in the early disease stages (2) to identify MCI individuals with 'prodromal Alzheimer's disease' that will progress to Alzheimer's disease at long-term clinical follow up, and to differentiate from both stable MCI cases and MCI people developing other dementias (3). Notably, a wealth of studies have also shown high agreement between CSF $A\beta42$ (and $A\beta42/40$ ratio) and amyloid PET positivity, with concordance figures of 90% or higher (4), which is in the same range as the concordance between different expert readers classifying amyloid PET scans as either positive or negative for brain amyloidosis (5). In other words, amyloid PET and CSF biomarkers can be used interchangeably in the clinic, leaving the clinician, together with the individual, the option to decide based on costs, expertise, availability, and risk estimations (radiation exposure vs. post lumbar puncture headache).

It should be noted that CSF T-tau and P-tau correlate closely within Alzheimer's disease and control populations (6), but the correlation is lost in diseases with marked neuronal damage but no tangles or tau pathology, such as acute stroke and Creutzfeldt-Jakob disease (7–9), supporting CSF T-tau as a neurodegeneration biomarker and that CSF P-tau reflects Alzheimer-type tau pathology. For unknown reasons, CSF P-tau seems specifically increased in Alzheimer's disease, and normal in other tauopathies, such as progressive supranuclear palsy and frontotemporal dementia.

Recent developments to standardise the core Alzheimer's disease CSF biomarkers include uniform procedures for the collection of CSF by lumbar puncture and so-called pre-analytical procedures, for example, the use of specific test tubes (to avoid unspecified loss of the protein biomarkers) for CSF collection (10), and the development methods for measurement of these Alzheimer's disease CSF biomarkers on fully automated lab analysers. As an example, the $A\beta1$–42 method on the Cobas Elecsys platform shows excellent performance and very low between-day variability (11), and the methods for T-tau and P-tau have even higher performance (12). These improvements are important to have exact and consistent readouts for the CSF Alzheimer's disease biomarkers in the clinical routine setting.

CSF biomarkers reflecting other pathogenic mechanisms in Alzheimer's disease include biomarkers for synaptic degeneration, which is an early phenomenon in Alzheimer's disease (13, 14) that is linked to cognitive symptoms (15, 16). One example is the post-synaptic protein neurogranin, that is found in the cortex and hippocampus, brain regions heavily affected in Alzheimer's disease (17, 18), and plays a role in memory formation (19, 20). Increased CSF neurogranin concentration is found in Alzheimer's disease dementia also in the early prodromal phase of disease (21), and high CSF neurogranin predicts future rate of neuronal degeneration (22). Interestingly, high CSF neurogranin is seemingly specific to Alzheimer's disease, while levels are normal in other neurodegenerative disorders such as frontotemporal dementia and progressive supranuclear palsy (23, 24).

In summary, the core CSF Alzheimer's disease biomarkers show very high diagnostic utility, are clinically well validated, and are available today on fully automated instruments that have excellent analytical performance. In many countries all over the world, these biomarkers now have a central place as diagnostic tests in routine clinical practice.

References

1. Blennow K, Hampel H, Weiner M, Zetterberg H. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. Nature reviews Neurology. 2010;6(3):131-44.

2. 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 neurology. 2016;15(7):673-84.

3. Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. Lancet neurology. 2006;5(3):228-34.

4. Blennow K, Mattsson N, Scholl M, Hansson O, Zetterberg H. Amyloid biomarkers in Alzheimer's disease. Trends in pharmacological sciences. 2015;36(5):297-309.

5. Hansson O, Seibyl J, Stomrud E, Zetterberg H, Trojanowski JQ, Bittner T, et al. CSF biomarkers of Alzheimer's disease concord with amyloid-beta PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzheimers Dement. 2018.

6. Sjogren M, Davidsson P, Tullberg M, Minthon L, Wallin A, Wikkelso C, et al. Both total and phosphorylated tau are increased in Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2001;70(5):624-30.

7. Hesse C, Rosengren L, Andreasen N, Davidsson P, Vanderstichele H, Vanmechelen E, et al. Transient increase in total tau but not phospho-tau in human cerebrospinal fluid after acute stroke. Neuroscience letters. 2001;297(3):187-90.

8. Riemenschneider M, Wagenpfeil S, Vanderstichele H, Otto M, Wiltfang J, Kretzschmar H, et al. Phospho-tau/total tau ratio in cerebrospinal fluid discriminates Creutzfeldt-Jakob disease from other dementias. Mol Psychiatry. 2003;8(3):343-7.

9. Skillback T, Rosen C, Asztely F, Mattsson N, Blennow K, Zetterberg H. Diagnostic performance of cerebrospinal fluid total tau and phosphorylated tau in Creutzfeldt-Jakob disease: results from the Swedish Mortality Registry. JAMA Neurol. 2014;71(4):476-83.

10. Hansson O, Batrla R, Brix B, Carrillo MC, Corradini V, Edelmayer RM, et al. The Alzheimer's Association international guidelines for handling of cerebrospinal fluid for routine clinical measurements of amyloid beta and tau. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2021.

11. Bittner T, Zetterberg H, Teunissen CE, Ostlund RE, Jr., Militello M, Andreasson U, et al. Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of beta-amyloid (1-42) in human cerebrospinal fluid. Alzheimers Dement. 2016;12(5):517-26.

12. Hansson O, Seibyl J, Stomrud E, Zetterberg H, Trojanowski JQ, Bittner T, et al. CSF biomarkers of Alzheimer's disease concord with amyloid-beta PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzheimer's & dementia: the journal of the Alzheimer's Association. 2018;14(11):1470-81.

13. Masliah E, Mallory M, Alford M, DeTeresa R, Hansen LA, McKeel DW, Jr., et al. Altered expression of synaptic proteins occurs early during progression of Alzheimer's disease. Neurology. 2001;56(1):127-9.

14. Scheff SW, Price DA, Schmitt FA, DeKosky ST, Mufson EJ. Synaptic alterations in CA1 in mild Alzheimer disease and mild cognitive impairment. Neurology. 2007;68(18):1501-8.

15. Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, et al. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol. 1991;30(4):572-80.

16. DeKosky ST, Scheff SW. Synapse loss in frontal cortex biopsies in Alzheimer's disease: correlation with cognitive severity. Annals of neurology. 1990;27(5):457-64.

17. Represa A, Deloulme JC, Sensenbrenner M, Ben-Ari Y, Baudier J. Neurogranin: immunocytochemical localization of a brain-specific protein kinase C substrate. J Neurosci. 1990;10(12):3782-92.

18. Guadano-Ferraz A, Vinuela A, Oeding G, Bernal J, Rausell E. RC3/neurogranin is expressed in pyramidal neurons of motor and somatosensory cortex in normal and denervated monkeys. J Comp Neurol. 2005;493(4):554-70.

19. Huang KP, Huang FL, Jager T, Li J, Reymann KG, Balschun D. Neurogranin/RC3 enhances long-term potentiation and learning by promoting calcium-mediated signaling. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2004;24(47):10660-9.

20. Wu J, Li J, Huang KP, Huang FL. Attenuation of protein kinase C and cAMP-dependent protein kinase signal transduction in the neurogranin knockout mouse. The Journal of biological chemistry. 2002;277(22):19498-505.

21. Kvartsberg H, Duits FH, Ingelsson M, Andreasen N, Ohrfelt A, Andersson K, et al. Cerebrospinal fluid levels of the synaptic protein neurogranin correlates with cognitive decline in prodromal Alzheimer's disease. Alzheimers Dement. 2015;11(10):1180-90.

22. Portelius E, Zetterberg H, Skillback T, Tornqvist U, Andreasson U, Trojanowski JQ, et al. Cerebrospinal fluid neurogranin: relation to cognition and neurodegeneration in Alzheimer's disease. Brain : a journal of neurology. 2015;138(Pt 11):3373-85.

23. Wellington H, Paterson RW, Portelius E, Tornqvist U, Magdalinou N, Fox NC, et al. Increased CSF neurogranin concentration is specific to Alzheimer disease. Neurology. 2016;86(9):829-35.

24. 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 neuropathologica. 2018;136(3):363-76.

Conclusions

Cerebrospinal fluid biomarkers provide reliable and clinically relevant diagnostic information in dementia cases of diagnostic uncertainly. Due to its lower cost, cerebrospinal fluid biomarker might constitute a viable diagnostic method in low- and middle-income countries. Importantly, the scalability of cerebrospinal fluid biomarkers seems a sustainable option for assessing patient eligibility for the upcoming disease-modifying interventions. Cerebrospinal fluid biomarker research developments bring hope for the diagnosis of non-Alzheimer's disease neurodegenerative processes underlying dementia.

Additional references

1. Atkinson AJ, Colburn WA, DeGruttola VG, DeMets DL, Downing GJ, Hoth DF, et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;69:89–95. https://doi.org/10.1067/mcp.2001.113989.

2. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's Dement 2018;14:535–62. https://doi.org/10.1016/j.jalz.2018.02.018.

3. Blennow K, Zetterberg H, Fagan AM. Fluid biomarkers in Alzheimer disease. Cold Spring Harb Perspect Med 2012;2:9. https://doi.org/10.1101/cshperspect.a006221.

4. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement 2011;7:263–9. https://doi.org/10.1016/j.jalz.2011.03.005.

5. Hansson O. Biomarkers for neurodegenerative diseases. Nat Med 2021;27:954–63. https://doi.org/10.1038/s41591-021-01382-x.

6. Hansson O, Lehmann S, Otto M, Zetterberg H, Lewczuk P. Advantages and disadvantages of the use of the CSF Amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's Disease. Alzheimer's Res Ther 2019;11:1–15. https://doi.org/10.1186/s13195-019-0485-0.

7. Mattsson N, Zetterberg H, Hansson O, Andreasen N, Parnetti L, Jonsson M, et al. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. JAMA – J Am Med Assoc 2009;302:385–93. https://doi.org/10.1001/jama.2009.1064.

8. Janelidze S, Stomrud E, Smith R, Palmqvist S, Mattsson N, Airey DC, et al. Cerebrospinal fluid p-tau217 performs better than p-tau181 as a biomarker of Alzheimer's disease. Nat Commun 2020;11:1. https://doi.org/10.1038/s41467-020-15436-0.

9. Ritchie C, Smailagic N, Noel-Storr AH, Ukoumunne O, Ladds EC, Martin S. CSF tau and the CSF tau/ABeta ratio for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev 2017;2017. https://doi.org/10.1002/14651858.CD010803.pub2.

10. Leuzy A, Cullen NC, Mattsson-Carlgren N, Hansson O. Current advances in plasma and cerebrospinal fluid biomarkers in Alzheimer's disease. Curr Opin Neurol 2021;34:266–74. https://doi.org/10.1097/WCO.0000000000000904.

11. Simonsen AH, Herukka SK, Andreasen N, Baldeiras I, Bjerke M, Blennow K, et al. Recommendations for CSF AD biomarkers in the diagnostic evaluation of dementia. Alzheimer's Dement 2017;13:274–84. https://doi.org/10.1016/j.jalz.2016.09.008.

12. Ismail Z, Black SE, Camicioli R, Chertkow H, Herrmann N, Laforce R, et al. Recommendations of the 5th Canadian Consensus Conference on the diagnosis and treatment of dementia. Alzheimer's Dement 2020;16:1182–95. https://doi.org/10.1002/alz.12105.

13. Hort J, O'Brien JT, Gainotti G, Pirttila T, Popescu BO, Rektorova I, et al. EFNS guidelines for the diagnosis and management of Alzheimer's disease. Eur J Neurol 2010;17:1236–48. https://doi.org/10.1111/j.1468-1331.2010.03040.x.

14. Ashton NJ, Janelidze S, Al Khleifat A, Leuzy A, van der Ende EL, Karikari TK, et al. A multicentre validation study of the diagnostic value of plasma neurofilament light. Nat Commun 2021;12. https://doi.org/10.1038/s41467-021-23620-z.