For reprint orders, please contact: reprints@futuremedicine.com

Cerebrospinal fluid biomarkers in neurodegenerative disorders

Thalia T Robey¹ & Peter K Panegyres^{*,1,2}

¹Neurodegenerative Disorders Research Pty Ltd, 4 Lawrence Avenue, West Perth, Western Australia 6005, Australia

²Clinical Professor of Neurology, The University of Western Australia, Perth, Australia

*Author for correspondence: Tel.: +61 8 9481 6293; Fax: +61 8 9481 6294; research@ndr.org.au

Neurodegenerative diseases represent a daunting challenge in clinical diagnosis and management. Biomarkers that might aid in the diagnosis of these devastating and globally important diseases are urgently sought and required. Here we describe the application and state of development of a range of cerebrospinal fluid biomarkers in common neurodegenerative disorders including Alzheimer's disease, frontotemporal dementia and prion diseases.

First draft submitted: 31 August 2018; Accepted for publication: 17 December 2018; Published online: 25 January 2019

Keywords: Alzheimer's disease • biomarker • cerebrospinal fluid • dementia • neurodegenerative disease

Alzheimer's disease

Cerebrospinal fluid (CSF) biomarkers and their use in neurodegenerative disorders represent an emerging area of research. The clinical use of CSF biomarkers for Alzheimer's disease (AD) is better supported than for other neurodegenerative diseases. CSF biomarkers are useful as screening tools and as supplementary information to diagnostic investigations but are lacking as diagnostic tools in isolation.

For AD, established markers are T-tau, P-tau and $A\beta_{42}$ [1]. CSF $A\beta_{42}$ is elevated, while CSF T-tau and P-tau are lowered [2]. Their significance results from their direct correspondence to the AD amyloid/tau hypothesis and evidence of effective clinical use. Of the markers discussed here, T-tau, P-tau and $A\beta_{42}$ are some of few to actually form part of diagnostic criteria; this triplet of biomarkers is part of both the International Working Group IWG-2 Criteria for AD and the National Institute on Aging-Alzheimer's Association (NIA-AA) Criteria for AD and mild cognitive impairment (MCI) resulting from AD [3]. In both criteria, CSF T-tau, P-tau and $A\beta_{42}$ are part of the same criterion as amyloid imaging, in allowance for dissociation between CSF biomarkers and imaging studies [3,4].

Recent studies have examined biomarker ratios and frequently found them to be superior to their individual constituents. The most prominent ratio is CSF $A\beta_{42}/A\beta_{40}$, which has demonstrated greater sensitivity and specificity for AD [2,5], greater accuracy in predicting abnormal amyloid deposition in patients with MCI [6], and greater correlation to amyloid imaging, than CSF $A\beta_{42}$ alone [7]. The CSF $A\beta_{42}/A\beta_{38}$ ratio has also demonstrated diagnostic promise in at least one study [6]. The same study also identified dissociations between $A\beta_{42}/A\beta_{40}$ and $A\beta_{42}/A\beta_{38}$ ratios, individual biomarkers ($A\beta_{42}$, $A\beta_{40}$ and $A\beta_{38}$) and findings on MRI (hippocampal atrophy, white matter lesions, etc.) [6]. As individual biomarkers, CSF $A\beta_{40}$ and CSF $A\beta_{38}$ have received little attention and there is no evidence to indicate that they are comparable to CSF $A\beta_{42}$. One study found correlation between levels of CSF $A\beta_{38}$ and CSF $A\beta_{40}$, indicating that they may be comparable to each other [8] – in light of dissociations between $A\beta_{42}/A\beta_{40}$ and $A\beta_{42}/A\beta_{38}$ ratios, this is curious. Correlations between elevated CSF $A\beta_{40}$ and CSF $A\beta_{38}$, and worsening gait variability have also been observed; this correlation did not extend to CSF $A\beta_{42}$ [9]. Perhaps CSF $A\beta_{42}$ is useful in screening and diagnosis while CSF $A\beta_{40}$ and CSF $A\beta_{38}$ are useful for screening and diagnosis when part of ratios, and useful for prognosis when used individually. Until there is further investigation of CSF $A\beta_{40}$, CSF $A\beta_{38}$, and their corresponding ratios with CSF $A\beta_{42}$, however, such statements remain conjecture.

T-tau has also been implemented into ratios; for instance, the CSF T-tau/ $A\beta_{42}$ ratio is able to predict progression from preclinical to clinical AD [2]. Findings regarding CSF T-tau ratios are limited, however, with the bulk of research focusing on $A\beta$ peptides. Recent developments have focused on the different forms of P-tau. CSF P-tau is measured in the form of either P-tau₁₈₁ or P-tau₂₃₁ (i.e., tau phosphorylated at the threonine 181 or 231 position,

respectively) [2,10]. Studies thus far identify P-tau₂₃₁ as the more accurate of the two [11]; however, recent work suggests that both forms of P-tau could have their own unique roles in diagnosis. Elevated CSF P-tau₂₃₁ has been investigated as a biomarker to differentiate AD from vascular dementia [12,13], but further work is required. Elevated CSF P-tau₁₈₁ has been suggested as a biomarker for suspected non-AD pathology; Pouclet-Courtmanche *et al.* identified normal CSF A β ₄₂, normal CSF A β ₄₂/A β ₄₀ and abnormal CSF P-tau₁₈₁ as a characteristic profile for suspected non-AD pathology in patients presenting with memory loss [14]. Further examination of such associations and dissociations in AD, AD variants and other neurodegenerative disorders whose presentations overlap with AD would further inform the use of CSF biomarkers in clinical settings.

Dissociation between CSF biomarkers and imaging studies has been observed. In the context of tau imaging, Mattson *et al.* observed that although tau deposition increased in progression from preclinical to clinical AD, CSF T-tau and P-tau remained static [15]. This ties in with others' observations that while imaging studies demonstrate progression, CSF biomarkers do not – they are 'static' [3]. For instance, many CSF biomarkers in AD (including A β ₄₂, T-tau and P-tau) have been able to predict progression from preclinical to clinical AD as they are already elevated in prodromal patients [16]. This success extends to the combination of CSF biomarkers with imaging [17] and the use of CSF biomarkers in the diagnosis of early-onset AD (AD in patients 65 years or younger) [18]. Further evaluation of how CSF biomarkers relate to imaging studies and time is required. Overall, the current evidence supports the use of CSF A β ₄₂, CSF T-tau and CSF P-tau as screening or diagnostic tools; if they do not change with time, little is to be gained beyond use at initial presentation.

Emerging biomarkers

Recent work has investigated the behaviour of biomarkers that are nonspecific to AD pathology. Study of these biomarkers and their relationships to the classical AD triplet could represent further improvement and efficacy in the clinical application of CSF biomarkers. Prominent examples of such biomarkers are YKL-40 (also known as CHI3L, YKL-40 is a marker of glial inflammation [19]), VILIP-1 (also known as VLP-1, a marker of neuronal damage [20]) and NFL (nonspecific marker of neurodegeneration [10,21]).

Elevated CSF YKL-40 has been most successful as a predictor of progression from MCI to clinical AD [16,22]. Elevated CSF YKL-40 has also been associated with pathological processes associated, or hypothesized to be associated, with AD; elevated CSF YKL-40 has been associated with markers of humoral immunity [22] and abnormal increases in blood-brain barrier permeability [22]. This perhaps indicates a role for CSF YKL-40 in clinical trials or research, while the precise clinical role of CSF YKL-40 remains uncertain. The same can be said of CSF VILIP-1 - findings of VILIP-1 in AD fall into two groups: increased levels or no change [10,22,23]. Associations between VILIP-1 and YKL-40 have also been observed [22]. Specificity of these markers for AD requires assessment.

CSF NFL has received significant attention in the literature across many neurodegenerative diseases, including AD. NFL forms part of the cytoskeleton and is released into the CSF when axons are damaged [21]; increased CSF NFL is thus a marker for neuronal injury and neurodegeneration [10,21]. Its utility in AD diagnosis is debatable: some studies identify significant increases in CSF NFL [10], whilst others observed no such increase once age and statistical corrections are considered [21]. Furthermore, the specificity of increased CSF NFL for AD is questionable, with CSF NFL showing increases in other neurodegenerative diseases [24,25]. Additionally, one study observed no correlation between CSF NFL and CSF A β ₄₂, indicating that NFL may indicate neurodegeneration independently of A β pathology [26]. CSF NFL has shown potential in distinguishing disease variants [27] but further work is required. The apparent nonspecificity of CSF NFL indicates that it may be more useful as a screening tool for neurodegenerative disease in general; however, more specific CSF biomarkers are already available as screening tools for several neurodegenerative diseases. Despite the attention it has received in the literature, the clinical utility of CSF NFL for AD (and other neurodegenerative diseases) remains questionable.

Beyond YKL-40, VILIP-1 and NFL, other emerging biomarkers include Ng (synaptic protein) and UCH-L1 (neuron-specific cell cycle enzyme). CSF Ng is significantly increased in AD [28]. Initial evidence indicates that this increase is AD-specific [29]. Studies found that CSF Ng could predict progression to clinical AD in MCI patients [30], and, in combination with T-tau, differentiate amnesic AD from AD variants [31]. CSF Ng has also been correlated with CSF T-tau and CSF A β ₄₂ [26], the deposition of tau neurofibrillary deposits [32], and the deposition of β -amyloid plaques [32]. CSF UCH-L1 has been found to increase in AD patients versus controls, patients with other dementias and patients with MCI [11]. UCH-L1 is also implicated in AD pathophysiology as a constituent of neurofibrillary tangles; however, the specificity of UCH-L1 to these tangles is uncertain [11,33]. CSF UCH-L1 also shows positive correlations with CSF P-tau and NSE, both markers of neurodegeneration [11].

Findings of CSF Ng and CSF UCH-L1 are sufficient to prompt further investigation, but insufficient to support clinical application at this time.

Many other potential CSF biomarkers have been investigated (e.g. NSE [34,35], CSF MCP-1, CSF/serum albumin ratios, vascular growth factors, and various forms of sAPP [1,10]) but findings have been insufficiently robust [10].

Frontotemporal dementia

Frontotemporal dementia (FTD) has three clinical subtypes: behavioural variant FTD, semantic dementia and progressive nonfluent aphasia. Overlapping clinical features create difficulties in clinical differentiation. These difficulties are further complicated by FTD's pathological heterogeneity (tau versus TDP-43). To this end, the biomarker with the most promise is CSF P-tau₁₈₁/T-tau; reduced CSF P-tau₁₈₁/T-tau is able to distinguish TDP-43-pathology from tau-pathology [36–38]. The proposed usage of CSF biomarkers in FTD is in distinguishing different FTD variants and distinguishing FTD from AD with frontal presentations. The classical AD triplet may be useful in distinguishing AD from FTD (particularly frontal AD), with the concentrations of A β ₄₂, T-tau and P-tau in FTD being comparable with controls [24]. Ratios may be more useful, with CSF A β ₄₂/P-tau₁₈₁ demonstrating the greatest ability to distinguish AD from FTD [39].

Nonspecific markers for FTD have had promising results. Findings of CSF YKL-40 and CSF NFL in FTD are comparable those in AD. CSF YKL-40 is elevated in FTD [40,41]. YKL-40 has also shown positive correlations with CSF T-tau [41], and one study has found CSF YKL-40 distinguished tau-positive patients from controls [42]. Few studies have compared CSF YKL-40 in different neurodegenerative diseases such as AD and FTD. One investigation found CSF YKL-40 levels in AD patients to be significantly higher than those with FTD and controls [42]. NFL has been the topic of considerable FTD research, with different applications suggesting a relationship to disease severity [43] and survival [44]. Similarly to AD, the specificity of CSF NFL to FTD remains debatable; however, one study found that increased CSF NFL levels in FTD patients could distinguish FTD from Lewy body disease, Parkinson's disease (PD) dementia, AD, FTD-associated motor neuron disease (MND); and behavioral variant FTD from progressive supranuclear palsy (PSP) [24]. CSF NFL cannot distinguish different FTD subtypes (clinical or pathological) [36]. It has also been suggested that CSF NFL can be used together with CSF YKL-40 and other markers to distinguish FTD from AD; at least one study has suggested the use of sAPP ratios with YKL-40 and NFL in separating FTD from AD [40]. Results of CSF sAPP as an individual FTD biomarker have been inconsistent and further study is required [24,40]. Further assessment of both markers is needed – inconsistencies and uncertainties of disease specificity limit clinical application of CSF YKL-40 and CSF NFL in FTD as well as AD.

Prion diseases

Prion diseases are fatal neurodegenerative diseases caused by the formation and propagation throughout the brain of misfolded proteins known as prions [45]. Typically, physiological PrP^C transforms into pathological PrP^{Sc}, producing disease [46]. Prion diseases include Creutzfeldt-Jakob Disease, kuru, fatal familial insomnia and others [45].

Recent studies have focused on measuring levels of prion protein, PrP^{Sc}, in CSF. To this end, a technique called real-time quaking-induced conversion (RT-QUIC) has been developed. The 'quaking' refers to intermittent agitation applied to a 96 well plate as part of the assay [47]. RT-QUIC offers improved sensitivity and specificity in comparison to nonspecific biomarkers [47]. RT-QUIC is able to detect the presence of PrP^{Sc} in biological samples such as CSF [47]. RT-QUIC can detect PrP^{Sc} in human CSF with sensitivities and specificities of 80–96% and 99–100%, respectively [48]; one study has successfully used RT-QUIC in the diagnosis of sporadic prion diseases [49]. RT-QUIC and CSF PrP^{Sc} demonstrate significant potential. Further assessment in clinical settings is still required prior to widespread application.

Prior to RT-QUIC, the focus was on nonspecific CSF biomarkers for prion disease. The most successful nonspecific marker is the 14-3-3 protein. 14-3-3 protein is a neuronal surface protein and CSF biomarker for neuronal cell death [50]. 14-3-3 protein has been useful as a surrogate marker of prion disease, but its specificity and sensitivity remain questionable [50]. The clinical utility of 14-3-3 protein may be improved by combination with other CSF biomarkers (A β ₄₂, T-tau, P-tau, NFL, etc.); however, research is still preliminary. CSF ratios of A β ₄₂, T-tau and P-tau have provided inconsistent results in the diagnosis of prion disease [51,52], and correlations between CSF T-tau, 14-3-3 and NFL have been found [53]. CSF T-tau and P-tau may be more useful than CSF A β ₄₂ in prion diseases. Associations with A β ₄₂ are tenuous – one study reported low CSF A β ₄₂ in the absence of A β plaques [51]. Again, further work is needed prior to confident clinical application.

Motor neuron disease

Though investigation into the clinical utility of CSF biomarkers in MND is still required, preliminary studies are promising. Of most prominent are neurofilament proteins – specifically NFL and pNFH [25,54]. Increased levels of NFL and pNFH have been consistently observed in CSF samples from patients with MND [25]. Similarly to AD, FTD and others, the specificity of elevated CSF NFL for MND remains uncertain. Furthermore, the absence of increased CSF NFL and/or pNFH is insufficient to rule out an MND diagnosis [25]. Both NFL and pNFH vary with rate and stage of disease progression [25], and are indistinguishable from controls in asymptomatic disease [55]. pNFH is less vulnerable to variations and artifacts in laboratory methods than NFL [56], and may be more useful. CSF TDP-43 might be more helpful [54]. Promising results have been found with lipids [57] and the Sonic Hedgehog protein (a morphogen involved in the development and maintenance of the CNS) [58].

Parkinson's disease

CSF biomarkers for PD have received little attention. Some nonspecific patterns have been identified: increased NFL, decreased α -synuclein and decreased levels of 3,4-dihydroxyphenylacetate (a dopamine metabolite) [59]. Other dopamine metabolites and the application of metabolomics have shown promise pending further investigations [59]. Amyloid, tau and oxidative stress markers may have prognostic use: amyloid and tau markers show relationships with cognitive decline; oxidative stress markers show correlations with duration and severity of disease [59].

Specific markers have been examined with minimal success. Studies have focused on gene markers such as protein deglycase DJ-1. *PARK7*, the gene encoding DJ-1, results in autosomal recessive early-onset PD [60]. Studies of CSF DJ-1 in PD have produced inconsistent results [60,61]. There has been suggestion of combining CSF DJ-1 with CSF T-tau and/or P-tau [62] but this has yet to be pursued. UCH-L1 (encoded by *PARK5*) and ubiquitin have also been investigated, also to limited success [63,64].

Other extrapyramidal syndromes

Extrapyramidal syndromes (EPS) include multiple system atrophy (MSA), corticobasal degeneration (CBD) and PSP. These diseases are of two pathological subtypes: α -synucleinopathies (MSA) and tauopathies (CBD, PSP) [65]. Their diagnosis is complicated by a wide spectrum of overlapping clinical features. CSF analysis may offer improvements to diagnosis. Magdalinou *et al.* found CSF NFL, sAPP α and α -synuclein to be helpful: NFL levels were higher in MSA, CBD and PSP than PD; sAPP α levels were higher in MSA, CBD and PSP than both PD and AD; α -synuclein was lower in MSA than PD [65]. Studies using NFL to characterize tauopathies from PD have been successful while those using P-tau and T-tau to differentiate tauopathies (PSP and CBD) from controls have produced conflicting results [24]. CSF DJ-1 and CSF T-tau/A β ₄₂ have been found to be useful in distinguishing MSA from PD [62,66]. Additionally, T-tau and A β ₄₂ were able to successfully discriminate CBD from the corticobasal syndrome variant of AD [66]. Other markers have shown promise (e.g., YKL-40), but further assessment is required [24]. Due to the limited literature on CSF biomarkers for EPS, clinical application is not yet practical.

Limitations

The primary limitation in this area is the unmet need to address procedural and methodological inconsistencies; inconsistent cut-off values, lack of assay standardization, overlapping case definition – further studies, with larger, representative samples, are required to overcome these obstacles.

Future perspective

Commonly cited future directions are the need for standardized cut-off values and improving methodological consistency across different laboratories. This report would like to expand on these and identify more specific gaps in knowledge that require attention. First, clearer understanding of which biomarkers are useful at screening, diagnosis and/or prognosis is required. Further research into the clinical utility of different combinations of markers and/or ratios for different diseases and clinical settings is also needed. By addressing these gaps in knowledge, it is possible that within the next decade characteristic CSF biomarker profiles may be developed for each neurodegenerative disease – this would be of great benefit to diagnosis and prognosis. Second, more comprehensive understanding of how CSF biomarkers and ratios associate or dissociate with the findings of imaging studies and other investigations is required. Third, there should be closer examination of how the relationships between CSF biomarkers/ratios and the findings of other investigations change with time. CSF biomarkers do not change with time [3] while imaging findings do – further evaluation of different temporal changes, as well as other investigations (blood biomarkers,

Figure 1. Cerebrospinal fluid biomarkers in neurodegenerative disorders. Red = useful.

Gold = promising, requires further study.

AD: Alzheimer's disease; EPS: Extrapyrimalidal syndrome; FTD: Frontotemporal dementia; MND: Motor neuron disease; NFL: Neurofilament light protein; pNFH: Phosphorylated neurofilament heavy chain; PD: Parkinson's disease.

	AD	FTD	Prion Disease	MND	PD	EPS
$A\beta_{42}/A\beta_{40}$	Red					
$A\beta_{42}$	Red					
T-tau	Red					
P-tau	Red					
NFL	Gold	Gold	Gold	Gold	Gold	
YKL-40	Gold	Gold				
VILIP-1	Gold					
P-tau ₁₈₁ /T-tau		Gold				
14-3-3 protein			Red			
PrP ^{Sc}			Red			
pNFH				Gold		
α -synuclein					Gold	Gold

functional and cognitive assessments, etc.) would be beneficial to our understanding of disease staging, progression and prognosis. Promising initial results have been observed with plasma T-tau [10], miRNA [67] and NFL [28], but further investigations are required. Finally, dissociation between ratios and individual markers must also be addressed; it would be beneficial to understand the relationships between individual markers, ratios and other investigations for different neurodegenerative diseases.

We think that more CSF biomarkers will be discovered, and their utility investigated such that a proteomic profile will be developed in every patient; this profile will be useful in diagnosis and prognosis. That is, personalized neurology, such as artificial intelligence using computer algorithms, will streamline diagnosis and treatment of neurodegenerative processes.

Conclusion

CSF biomarkers have been investigated to varying degrees for many neurodegenerative disorders, as summarized in Figure 1. Nonspecific markers such as YKL-40 and NFL have demonstrated potential in AD, FTD, prion diseases, MND, PD and EPS, but further work is needed prior to clinical application. Specific markers have been more successful for AD ($A\beta_{42}$, T-tau and P-tau) and prion diseases (PrP^{Sc}). Ratios such as CSF $A\beta_{42}/A\beta_{40}$ may be superior to their individual constituents, pending further investigation.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Open access

This work is licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 Unported License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

Executive summary

- There are many obstacles to overcome in the diagnosis of neurodegenerative diseases. Identifying characteristic cerebrospinal fluid (CSF) biomarker profiles would be highly beneficial to overcoming these obstacles; however, many gaps and inconsistencies in the literature remain.

Alzheimer's disease

- Currently, CSF biomarkers have the most relevance to Alzheimer's disease (AD). AD is characterized by elevated CSF $A\beta_{42}$, decreased CSF T-tau and decreased CSF P-tau. Ratios such as CSF $A\beta_{42}/A\beta_{40}$ are increasingly prevalent and likely to supersede their individual constituents.
- CSF biomarkers do not show progression, while imaging studies do. CSF biomarkers become abnormal in early disease stages and remain static from then on, promoting their use as screening or diagnostic tools but not as prognostic tools. Further work is required.
- Markers that are not specific to AD disease processes, such as YKL-40, VILIP-1, NFL, Ng, UCH-L1 and others, are becoming more popular but the specificity of their changes to AD, and how these changes relate to classical AD markers, is unknown.

Frontotemporal dementia

- The struggle to identify specific markers for frontotemporal dementia is worsened by the multiple clinical and pathological subtypes of frontotemporal dementia. Some success has been found with tau ratios, for example, CSF P-tau₁₈₁/T-tau, but further work is required.
- Results have been more promising with combinations of markers such as YKL-40 and NFL. The applicability of these results is limited by unclear case definitions and lack of reproduced findings in the literature.

Prion disease

- Success has been found with the development of a new assay technique called real-time quaking-induced conversion, which is able to detect pathological prion proteins (PrP^{Sc}) in biological samples such as CSF.
- 14-3-3 protein has been a popular biomarker for prion disease; however, its specificity and sensitivity are questionable. Preliminary findings indicate that the utility of 14-3-3 protein may be improved by combining 14-3-3 with other biomarkers (e.g. $A\beta_{42}$, T-tau, NFL, etc.).

Motor neuron disease

- Little attention has been given to CSF biomarkers for motor neuron disease. The most promising are NFL and pNFH. The specificity of elevated NFL and elevated pNFH for motor neuron disease is uncertain.
- Other biomarkers such as lipids and Sonic Hedgehog protein have had promising initial results.

Parkinson's disease

- It has been difficult to identify CSF biomarkers for Parkinson's disease. Some patterns with nonspecific markers such as NFL and α -synuclein have been observed, but further work is required. It has also been suggested that oxidative stress markers, $A\beta_{42}$, T-tau or P-tau could be used.
- There have been attempts to use specific CSF biomarkers for Parkinson's disease-associated genes (e.g. *PARK5*, *PARK7*), with limited success.

Other extrapyramidal syndromes

- This group of neurodegenerative diseases is characterized by differing pathologies (α -synucleinopathies, tauopathies) and overlapping clinical features. Some attempts have been made to identify patterns of both specific and nonspecific biomarkers but findings are yet to be reproduced.

Limitations

- Unclear definitions and inconsistencies surrounding clinical features, cut-off values and assay techniques limit the generalization and clinical applicability of CSF biomarkers in neurodegenerative diseases.

Future perspective

- Clearer understanding of at which stage of diagnosis each biomarker(s) is useful is required.
- Minimal research has been done comparing different combinations of biomarkers and ratios for each neurodegenerative disease. It is important to engage in such comparisons if characteristic biomarker profiles for each disorder are to be developed.
- Understanding of how CSF biomarkers relate to other investigations, and how these relationships change with time, are needed. This would clarify the use of CSF biomarkers at various stages of diagnosis and/or prognosis.

Conclusion

- CSF biomarkers have been investigated to varying degrees of thoroughness for a range of neurodegenerative disorders.
- Nonspecific markers such as YKL-40 and NFL show potential across many neurodegenerative disorders. Profiles of these nonspecific markers in each neurodegenerative disorder have yet to be developed.
- Specific markers have been identified for AD ($A\beta_{42}$, T-tau and P-tau) and prion diseases (PrP^{Sc}).

References

Papers of special note have been highlighted as: • of interest

1. Burchell JT, Panegyres PK. Novel CSF biomarkers for Alzheimer's disease. *Future Neurol.* 10(6), 511–514 (2015).
2. 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.* 3 CD010803 (2017).
3. Parnetti L, Eusebi P. Cerebrospinal fluid biomarkers in Alzheimer's disease: an invaluable tool for clinical diagnosis and trial enrichment. *J. Alzheimer's Dis.* 64(s1), S281–S287 (2018).
4. Wang HF, Tan L, Cao L *et al.* Application of the IWG-2 diagnostic criteria for Alzheimer's disease to the ADNI. *J. Alzheimer's Dis.* 51(1), 227–236 (2016).
5. Blanco-Cantó ME, Monge-Argilés JA, Pérez-Cejuela C *et al.* Diagnostic validity comparison between criteria based on CSF Alzheimer's disease biomarkers. *Am. J. Alzheimer's Dis. Other Dement.* 32(2), 101–107 (2017).
6. Janelidze S, Zetterberg H, Mattsson N *et al.* CSF Abeta42/Abeta40 and Abeta42/Abeta38 ratios: better diagnostic markers of Alzheimer disease. *Ann. Clin. Transl. Neurol.* 3(3), 154–165 (2016).
7. Leuzy ACK, Pannee J, Hasselbalch S, *et al.* Improved concordance between [11C]PIB PET and CSF AB42 using AB42/AB40: findings from a multicenter European memory clinic population. *Neurobiol. Aging* 39(Suppl. 1), S18 (2016).
8. Gabelle A, Roche S, Geny C *et al.* Correlations between soluble alpha/beta forms of amyloid precursor protein and Abeta38, 40, and 42 in human cerebrospinal fluid. *Brain Res.* 1357, 175–183 (2010).
9. Koychev I, Galna B, Zetterberg H *et al.* Abeta42/Abeta40 and Abeta42/Abeta38 ratios are associated with measures of gait variability and activities of daily living in mild Alzheimer's disease: a pilot study. *J. Alzheimer's Dis.* 65(4), 1377–1383 (2018).
10. Olsson B, Lautner R, Andreasson U *et al.* CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *Lancet Neurol.* 15(7), 673–684 (2016).
11. Ohrfelt A, Johansson P, Wallin A *et al.* Increased cerebrospinal fluid levels of ubiquitin carboxyl-terminal hydrolase L1 in patients with Alzheimer's disease. *Dement. Geriatr. Cogn. Dis. Extra* 6(2), 283–294 (2016).
12. Wang H, Wang T, Qian S, Ba L, Lin Z, Xiao S. A pilot longitudinal study on cerebrospinal fluid (CSF) tau protein in Alzheimer's disease and vascular dementia. *Shanghai Arch. Psychiatry* 28(5), 271–279 (2016).
13. Kidemet-Piskac S, Babic Leko M, Blazekovic A *et al.* Evaluation of cerebrospinal fluid phosphorylated tau231 as a biomarker in the differential diagnosis of Alzheimer's disease and vascular dementia. *CNS Neurosci. Ther.* 24(8), 734–740 (2018).
14. Pouclet-Courtemanche HNT, Schraen S, Pasquier F, Dumurgier J, Paquet C, Lebouvier T. Clinical profile of patients with normal CSF ab42 and Ab42/Ab40 ratio, yet abnormal CSF 181p-tau: a snap story. *Alzheimer's Dementia* 13(7), P343 (2017).
- **Examines dissociations between individual markers and ratios and investigates how these can be used to create characteristic CSF biomarker profiles.**
15. Mattsson N, Smith R, Strandberg O *et al.* Comparing (18)F-AV-1451 with CSF t-tau and p-tau for diagnosis of Alzheimer's disease. *Neurology* 90(5), e388–e395 (2018).
- **Examines dissociations between markers and imaging. Further investigation of this topic could inform diagnostic criteria and pathological understanding.**
16. Antonell A, Mansilla A, Rami L *et al.* Cerebrospinal fluid level of YKL-40 protein in preclinical and prodromal Alzheimer's disease. *J. Alzheimer's Dis.* 42(3), 901–908 (2014).
17. Galasko DR, Shaw LM. CSF biomarkers for Alzheimer disease – approaching consensus. *Nat. Rev. Neurol.* 13, 131 (2017).
18. Faull M, Ching SY, Jarmolowicz AI, Beilby J, Panegyres PK. Comparison of two methods for the analysis of CSF Abeta and tau in the diagnosis of Alzheimer's disease. *Am. J. Neurodegener. Dis.* 3(3), 143–151 (2014).
19. Bonneh-Barkay D, Bissel SJ, Wang G *et al.* YKL-40, a marker of simian immunodeficiency virus encephalitis, modulates the biological activity of basic fibroblast growth factor. *Am. J. Pathol.* 173(1), 130–143 (2008).
20. Kirkwood CM, Macdonald ML, Schempf TA *et al.* Altered levels of Visinin-Like Protein 1 correspond to regional neuronal loss in Alzheimer's disease and frontotemporal lobar degeneration. *J. Neuropathol. Exp. Neurol.* 75(2), 175–182 (2016).
- **Examines how levels of VILIP-1 differ in different brain regions and posit VILIP-1 as a marker of neuronal loss in the entorhinal cortex.**
21. Gaiottino J, Norgren N, Dobson R *et al.* Increased neurofilament light chain blood levels in neurodegenerative neurological diseases. *PLoS ONE* 8(9), e75091 (2013).
22. Muszynski P, Kulczynska-Przybik A, Borawska R *et al.* The relationship between markers of inflammation and degeneration in the central nervous system and the blood-brain barrier impairment in Alzheimer's disease. *J. Alzheimer's Dis.* 59(3), 903–912 (2017).
- **Examines relationships between nonspecific markers for Alzheimer's disease (AD) and their relation to AD disease processes.**
23. Kester MI, Teunissen CE, Sutphen C *et al.* Cerebrospinal fluid VILIP-1 and YKL-40, candidate biomarkers to diagnose, predict and monitor Alzheimer's disease in a memory clinic cohort. *Alzheimer's Res. Ther.* 7(1), 59 (2015).

24. Oeckl P, Steinacker P, Feneberg E, Otto M. Neurochemical biomarkers in the diagnosis of frontotemporal lobar degeneration: an update. *J. Neurochem.* 138(Suppl 1), 184–192 (2016).
25. Li D, Shen D, Tai H, Cui L. Neurofilaments in CSF as diagnostic biomarkers in motor neuron disease: a meta-analysis. *Front. Aging Neurosci.* 8, 290 (2016).
26. Mattsson N, Insel PS, Palmqvist S *et al.* Cerebrospinal fluid tau, neurogranin, and neurofilament light in Alzheimer's disease. *EMBO Mol. Med.* 8(10), 1184–1196 (2016).
27. Abu-Rumeileh S, Capellari S, Stanzani-Maserati M *et al.* The CSF neurofilament light signature in rapidly progressive neurodegenerative dementias. *Alzheimer's Res. Ther.* 10(1), 3 (2018).
28. Blennow K. A review of fluid biomarkers for alzheimer's disease: moving from CSF to blood. *Neurol. Ther.* 6(Suppl 1), 15–24 (2017).
29. Wellington H, Paterson RW, Portelius E *et al.* Increased CSF neurogranin concentration is specific to Alzheimer disease. *Neurology* 86(9), 829–835 (2016).
30. Kvartsberg H, Duits FH, Ingelsson M *et al.* Cerebrospinal fluid levels of the synaptic protein neurogranin correlates with cognitive decline in prodromal Alzheimer's disease. *Alzheimer's Dement.* 11(10), 1180–1190 (2015).
31. Wellington H, Paterson RW, Suarez-Gonzalez A *et al.* CSF neurogranin or tau distinguish typical and atypical Alzheimer disease. *Ann. Clin. Transl. Neurol.* 5(2), 162–171 (2018).
- **Examines both classical and emerging CSF biomarkers for AD and how they can distinguish AD variants.**
32. Portelius E, Olsson B, Hoglund K *et al.* Cerebrospinal fluid neurogranin concentration in neurodegeneration: relation to clinical phenotypes and neuropathology. *Acta Neuropathol.* 136(3), 363–376 (2018).
33. Wang Q, Woltjer RL, Cimino PJ *et al.* Proteomic analysis of neurofibrillary tangles in Alzheimer disease identifies GAPDH as a detergent-insoluble paired helical filament tau binding protein. *FASEB J.* 19(7), 869–871 (2005).
34. Haque A, Polcyn R, Matzelle D, Banik NL. New insights into the role of neuron-specific enolase in neuro-inflammation, neurodegeneration and neuroprotection. *Brain Sci.* 8(2), 33 (2018).
35. Schmidt FM, Mergl R, Stach B, Jahn I, Gertz HJ, Schonknecht P. Elevated levels of cerebrospinal fluid neuron-specific enolase (NSE) in Alzheimer's disease. *Neurosci. Lett.* 570, 81–85 (2014).
36. Meeter LHH, Vijverberg EG, Del Campo M *et al.* Clinical value of neurofilament and phospho-tau/tau ratio in the frontotemporal dementia spectrum. *Neurology* 90(14), e1231–e1239 (2018).
37. Hu WT, Watts K, Grossman M *et al.* Reduced CSF p-Tau181 to Tau ratio is a biomarker for FTLT-TDP. *Neurology* 81(22), 1945–1952 (2013).
38. Borroni B, Benussi A, Archetti S *et al.* Csf p-tau181/tau ratio as biomarker for TDP pathology in frontotemporal dementia. *Amyotroph. Lateral Scler. Front. Degener.* 16(1-2), 86–91 (2015).
39. Vergallo A, Carlesi C, Pagni C *et al.* A single center study: Abeta42/p-Tau181 CSF ratio to discriminate AD from FTD in clinical setting. *Neurol. Sci.* 38(10), 1791–1797 (2017).
40. Alcolea D, Vilaplana E, Suarez-Calvet M *et al.* CSF sAPPbeta, YKL-40, and neurofilament light in frontotemporal lobar degeneration. *Neurology* 89(2), 178–188 (2017).
41. Teunissen CE, Elias N, Koel-Simmelink MJ *et al.* Novel diagnostic cerebrospinal fluid biomarkers for pathologic subtypes of frontotemporal dementia identified by proteomics. *Alzheimer's Dement.* 2, 86–94 (2016).
42. Baldacci F, Toschi N, Lista S *et al.* Two-level diagnostic classification using cerebrospinal fluid YKL-40 in Alzheimer's disease. *Alzheimer's Dement.* 13(9), 993–1003 (2017).
43. Scherling CS, Hall T, Berisha F *et al.* Cerebrospinal fluid neurofilament concentration reflects disease severity in frontotemporal degeneration. *Ann. Neurol.* 75(1), 116–126 (2014).
44. Skillback T, Mattsson N, Blennow K, Zetterberg H. Cerebrospinal fluid neurofilament light concentration in motor neuron disease and frontotemporal dementia predicts survival. *Amyotroph. Lateral Scler. Front. Degener.* 18(5-6), 397–403 (2017).
45. Aguzzi A, Zhu C. Microglia in prion diseases. *J. Clin. Investig.* 127(9), 3230–3239 (2017).
46. Aguzzi A, Nuvolone M, Zhu C. The immunobiology of prion diseases. *Nat. Rev. Immunol.* 13(12), 888–902 (2013).
47. Atarashi R, Sano K, Satoh K, Nishida N. Real-time quaking-induced conversion: a highly sensitive assay for prion detection. *Prion* 5(3), 150–153 (2011).
48. Kang HE, Mo Y, Abd Rahim R, Lee HM, Ryou C. Prion diagnosis: application of real-time quaking-induced conversion. *Biomed. Res. Int.* 2017(1), 1-8 (2017).
49. Satoh K, Atarashi R, Nishida N. Real-time quaking-induced conversion for diagnosis of prion disease. *Methods Mol. Biol.* 1658, 305–310 (2017).
50. Matsui Y, Satoh K, Miyazaki T *et al.* High sensitivity of an ELISA kit for detection of the gamma-isoform of 14–3–3 proteins: usefulness in laboratory diagnosis of human prion disease. *BMC Neurol.* 11, 120 (2011).

51. Lattanzio F, Abu-Rumeileh S, Franceschini A *et al.* Prion-specific and surrogate CSF biomarkers in Creutzfeldt-Jakob disease: diagnostic accuracy in relation to molecular subtypes and analysis of neuropathological correlates of p-tau and Abeta42 levels. *Acta Neuropathol.* 133(4), 559–578 (2017).
52. Abu Rumeileh S, Lattanzio F, Stanzani Maserati M, Rizzi R, Capellari S, Parchi P. Diagnostic accuracy of a combined analysis of cerebrospinal fluid t-PrP, t-tau, p-tau, and Abeta42 in the differential diagnosis of Creutzfeldt-Jakob disease from Alzheimer's disease with emphasis on atypical disease variants. *J. Alzheimer's Dis.* 55(4), 1471–1480 (2017).
53. Zerr I, Schmitz M, Karch A *et al.* Cerebrospinal fluid neurofilament light levels in neurodegenerative dementia: evaluation of diagnostic accuracy in the differential diagnosis of prion diseases. *Alzheimer's Dement.* 14(6), 751–763 (2018).
54. Oberstadt M, Classen J, Arendt T, Holzer M. TDP-43 and cytoskeletal proteins in ALS. *Mol. Neurobiol.* 55(4), 3143–3151 (2018).
55. Weydt P, Oeckl P, Huss A *et al.* Neurofilament levels as biomarkers in asymptomatic and symptomatic familial amyotrophic lateral sclerosis. *Ann. Neurol.* 79(1), 152–158 (2016).
56. Li S, Ren Y, Zhu W, Yang F, Zhang X, Huang X. Phosphorylated neurofilament heavy chain levels in paired plasma and CSF of amyotrophic lateral sclerosis. *J. Neurol. Sci.* 367, 269–274 (2016).
57. Blasco H, Veyrat-Durebex C, Bocca C *et al.* Lipidomics reveals cerebrospinal-fluid signatures of ALS. *Sci. Rep.* 7(1), 17652 (2017).
58. Drannik A, Martin J, Peterson R, Ma X, Jiang F, Turnbull J. Cerebrospinal fluid from patients with amyotrophic lateral sclerosis inhibits Sonic Hedgehog function. *PLoS ONE* 12(2), e0171668 (2017).
59. Andersen AD, Binzer M, Stenager E, Gramsbergen JB. Cerebrospinal fluid biomarkers for Parkinson's disease – a systematic review. *Acta Neurol. Scand.* 135(1), 34–56 (2017).
60. Jimenez-Jimenez FJ, Alonso-Navarro H, Garcia-Martin E, Agundez JA. Cerebrospinal fluid biochemical studies in patients with Parkinson's disease: toward a potential search for biomarkers for this disease. *Front. Cell Neurosci.* 8, 369 (2014).
61. Hong Z, Shi M, Chung KA *et al.* DJ-1 and alpha-synuclein in human cerebrospinal fluid as biomarkers of Parkinson's disease. *Brain* 133(Pt 3), 713–726 (2010).
62. Herbert MK, Eeftens JM, Aerts MB *et al.* CSF levels of DJ-1 and tau distinguish MSA patients from PD patients and controls. *Parkinsonism Relat. Disord.* 20(1), 112–115 (2014).
63. Sjodin S, Hansson O, Ohrfelt A *et al.* Mass spectrometric analysis of cerebrospinal fluid ubiquitin in Alzheimer's disease and Parkinsonian disorders. *Proteom. Clin. Appl.* 11(11–12), (2017).
64. Magdalinou N, Lees AJ, Zetterberg H. Cerebrospinal fluid biomarkers in parkinsonian conditions: an update and future directions. *J. Neurol. Neurosurg. Psychiatry* 85(10), 1065–1075 (2014).
65. Magdalinou NK, Paterson RW, Schott JM *et al.* A panel of nine cerebrospinal fluid biomarkers may identify patients with atypical parkinsonian syndromes. *J. Neurol. Neurosurg. Psychiatry* 86(11), 1240–1247 (2015).
66. Constantinides VC, Paraskevas GP, Emmanouilidou E *et al.* CSF biomarkers beta-amyloid, tau proteins and a-synuclein in the differential diagnosis of Parkinson-plus syndromes. *J. Neurol. Sci.* 382, 91–95 (2017).
67. Kumar S, Reddy PH. Are circulating microRNAs peripheral biomarkers for Alzheimer's disease? *Biochim. Biophys. Acta* 1862(9), 1617–1627 (2016).