CSF in the dementias

Henrik Zetterberg[1,2], Jonathan D Rohrer[3] and Jonathan M Schott[3]

[1]*Clinical Neurochemistry Laboratory, Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden*

[2]*Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, UK*

[3]*Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK*

Corresponding author:
Henrik Zetterberg, MD, PhD
Institute of Neuroscience and Physiology
Department of Psychiatry and Neurochemistry
The Sahlgrenska Academy at the University of Gothenburg
S-431 80 Mölndal
SWEDEN
Tel (office): +46 31 3430142
Tel (cell): +46 768 672647
Tel (secretary): +46 31 3430025
Fax: +46 31 3432426
E-mail: henrik.zetterberg@gu.se

Abstract

Alzheimer's disease, vascular dementia, dementia with Lewy bodies and frontotemporal dementia are the most common central nervous system disorders that cause progressive neurocognitive dysfunction and ultimately dementia. Here, we give an overview of the current state of practice and research regarding CSF biomarkers for these disorders. The chapter discusses both established and upcoming biomarkers and details, wherever appropriate, clinical use and differential diagnostics aspects.

Abbreviations

AD	Alzheimer's disease
fAD	Familial AD
VaD	Vascular dementia
DLB	Dementia with Lewy bodies
FTD	Frontotemporal dementia
CJD	Creutzfeldt-Jakob disease
MCI	Mild cognitive impairment
APP	Amyloid precursor protein
sAPPα	Soluble APP alpha
sAPPβ	Soluble APP beta
CNS	Central nervous system
CSF	Cerebrospinal fluid
T-tau	Total-tau
P-tau	Phospho-tau
Aβ42	Amyloid β 42
NFL	Neurofilament light
CCL2	C-C chemokine ligand 2
TREM2	Triggering receptor expressed on myeloid cells 2
CV	Coefficient of variation
HIV	Human immunodeficiency virus
QC	Quality control
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
ELISA	Enzyme-linked immunosorbent assay

Introduction

Dementias constitute a broad category of brain diseases that cause a gradual decrease in cognitive functioning. The most common type of dementia is Alzheimer's disease (AD), which makes up 50% to 70% of cases (Winblad et al., 2016). Other common types include vascular dementia (VaD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD). Less common causes include Parkinson's disease dementia (PDD), atypical parkinsonian syndromes, a wide range of metabolic and infectious causes including HIV-associated dementia (HAD), and Creutzfeldt-Jakob disease (CJD). A dementia diagnosis is usually based on history of the illness, the pattern of cognitive deficits, with investigations including, *e.g.*, blood work used to rule out other possible causes, and imaging both to rule out alternative diagnoses and to provide positive evidence for a given diagnosis. Specific dementia diagnoses can be made using clinical criteria supplemented by biomarkers, but a definite diagnosis requires autopsy confirmation, based on the fact that each of the degenerative dementia-causing brain disorders is characterised by more or less distinct neuropathology. A striking feature is that most degenerative dementias show aggregates or inclusions of specific proteins in the brain extracellular matrix or within neurons or other cell types of the brain. There is however also a considerable degree of cerebral multimorbidity suggesting that pathologically deposited proteins may interact and are influenced by other factors, in particular cerebrovascular disease, to promote cognitive decline and other clinical symptoms (Jellinger and Attems, 2015).

Cerebrospinal fluid (CSF) may be used in two broad ways in the investigation of dementia. First, CSF cell count, CSF to serum albumin ratio (a blood-brain barrier test) and IgG- and IgM-indices may be used to exclude neuroinflammatory and neuroinfectious disorders. Second, molecular markers of different pathologies may be measured in the CSF. This is where this book chapter has its emphasis. Molecular CSF markers of the major dementia-causing CNS diseases are reviewed below both in regards to their use in clinical practice and in relation to current state of research.

CSF biomarkers for Alzheimer's disease

Key molecular pathways involved

Neuropathologically, AD is characterised by neuronal loss in specific brain regions, intraneuronal neurofibrillary tangles composed of aggregated and often hyperphosphorylated tau protein, and extracellular neuritic plaques – deposits of amyloid β peptide [Aβ], ending at amino acid 42 (Blennow et al., 2006). Additionally, synapse loss (Terry et al., 1991) and microglial activation (Ulrich and Holtzman, 2016) have been suggested as integral parts of typical AD pathology.

CSF Aβ42

Initially, and following the identification of aggregation-prone Aβ proteins ending at amino acids 40 and 42 in senile plaques (Masters et al., 1985), Aβ production was thought to be an abnormal side-product of amyloid precursor protein (APP) metabolism invariably associated with AD. The natural secretion of Aβ from untransfected primary cells therefore came as a surprise (Haass et al., 1992). Since then, it has been established that APP can enter at least three proteolytic clearance pathways: (i) amyloidogenic processing that primarily leads to production of Aβ42 and Aβ40 (but also some shorter, less aggregation-prone fragments) by successive β- and γ-secretase cleavage; (ii) non-amyloidogenic processing that leads to production of sAPPα and possibly also a C-terminal fragment called p3; and (iii) another non-amyloidogenic processing pathway involving concerted cleavages of APP by β- and α-secretase resulting in production of Aβ1-14/15/16 fragments at the expense of longer Aβ fragments (Portelius et al., 2011).

The first enzyme-linked immunosorbent assay (ELISA) for CSF Aβ42 was published in 1995 (Motter et al., 1995). Using this technique, AD patients were shown to have reduced levels of CSF Aβ42, a finding which has since been replicated and verified in hundreds of papers (Olsson et al., 2016). This reduction is thought to reflect Aβ42 sequestration in senile plaques in the brain, as evidenced by both autopsy and *in vivo* imaging studies (Strozyk et al., 2003; Fagan et al., 2006; Forsberg et al., 2008; Seppala et al., 2012; Weston et al., 2015; Palmqvist et al., 2014). In 1999, the first paper showing a reduction in CSF Aβ42 in patients with mild cognitive impairment (MCI) who later developed AD dementia was published (Andreasen et al., 1999). Since then, numerous studies have verified that low CSF Aβ42 levels are highly predictive of future AD, both in MCI (Hansson et al., 2006; Shaw et al., 2009; Visser et al., 2009; Buchhave et al., 2012) and cognitively normal cohorts (Skoog et al., 2003; Fagan et al., 2009; Gustafson et al., 2007). Causal mutations aside, CSF Aβ42 remains the earliest

biomarker currently available in AD, and as a result CSF Aβ42 is now incorporated into new criteria for the diagnosis of AD, including the pre-dementia stages (Dubois et al., 2014). Low CSF Aβ42 concentrations in the absence of senile plaques have also been reported in neuroinflammatory conditions, *e.g.*, bacterial meningitis (Sjogren et al., 2001b), multiple sclerosis (Mattsson et al., 2009a), human immunodeficiency virus (HIV)-associated dementia (Gisslen et al., 2009) and Lyme neuroborreliosis (Mattsson et al., 2010), and are often accompanied by biomarker evidence of a general reduction in APP metabolites, *e.g.*, secreted forms of APP, which is not typical of AD (Rosen et al., 2013).

Besides Aβ42, several other Aβ isoforms are present in CSF. The most abundant variant in CSF is Aβ40, which is relatively unchanged in AD. The ratio of CSF Aβ42 to Aβ40 has been suggested to have stronger diagnostic accuracy for AD compared with CSF Aβ42 alone (Schoonenboom et al., 2005; Wiltfang et al., 2007).

CSF T-tau

The first CSF total tau (T-tau) assay was published in 1993 (Vandermeeren et al., 1993). This was a sandwich ELISA in which a monoclonal antibody against the mid-domain of tau was combined with a polyclonal anti-tau antiserum. Two years later, the first assay based on three mid-region monoclonal antibodies, which recognises all tau isoforms irrespective of phosphorylation state, was published (Blennow et al., 1995). Using this assay, AD patients were shown to have clearly elevated T-tau levels (Vandermeeren et al., 1993; Blennow et al., 1995), a finding that has been replicated in hundreds of papers, using several different assays, in many different clinical contexts (Olsson et al., 2016). It has been shown that CSF T-tau levels correlate with imaging measures of hippocampal atrophy (Wang et al., 2012) and grey matter degeneration (Glodzik et al., 2012), findings in keeping with the known high expression of tau in thin unmyelinated axons of the cortex (Trojanowski et al., 1989). In response to acute brain injury, CSF T-tau levels are dynamic; they increase during the first few days following injury and stay elevated for a few weeks until they normalise (Hesse et al., 2001; Zetterberg et al., 2006). This has led to the view that elevated CSF T-tau levels reflect ongoing axonal degeneration, which in turn may indicate disease activity. Indeed, CSF T-tau predicts the rapidity of the clinical course in AD; the higher levels, the more rapid clinical disease progression (Wallin et al., 2010). Accordingly, in severe and rapid neurodegeneration,

e.g., as in CJD, CSF T-tau elevations orders of magnitude higher than in typical AD are seen (Sanchez-Juan et al., 2007; Skillback et al., 2014b).

Two recent discoveries have made the tau biomarker field more complex. These include: (i) the finding that tau secretion from cultured cells (Saman et al., 2012) and mouse neurons (Maia et al., 2013) may be stimulated by Aβ in the absence of neuronal death (Maia et al., 2013); and (ii) that most of the tau in CSF seems to be fragmented (Meredith et al., 2013). Tau secretion in the absence of neurodegeneration is not unexpected as it has been known for decades that tau is present in the CSF of healthy individuals (Blennow et al., 2010). Nonetheless this raises some important issues from a practical perspective as it confirms that tau elevation cannot simply be considered a surrogate marker of neurodegeneration. Moreover, the mechanism of tau elevation in AD may well be at least partially independent of neuronal death. The latter would be consistent with tau changes seen in other forms of brain injury and the observation of intraneuronal increase in tau expression following acute experimental brain injury in animals (Uryu et al., 2007).

The finding that most CSF tau seems to be in fragmented forms is consistent with well established evidence that endogenous tau fragments are found in tangles (Wischik et al., 1988). It may also explain why it has been important to have capture and detection antibodies located closely to each other in T-tau assays, and why combinations of distally located N- and C-terminal antibodies do not work (Meredith et al., 2013). The clinical significance of these fragments is not known and it remains challenging to accomplish a reliable quantification, including determination of reference samples.

CSF P-tau

The first CSF assay for phosphorylated tau (P-tau), the form of tau that is believed to show the closest association with neurofibrillary tangle load, was published in 1995 (Blennow et al., 1995). Since then, a variety of P-tau assays measuring different forms of phosphorylated tau proteins have been developed (Hampel et al., 2004). Broadly speaking, these assays correlate well with one another, and show similar findings in AD (Hampel et al., 2004). CSF P-tau levels correlate with neurofibrillary tangle pathology in AD (Buerger et al., 2006; Seppala et al., 2012), but a major outstanding research question is why other tauopathies, including some forms of FTD and progressive supranuclear palsy, do not show P-tau elevation, at least not as systematically as seen in AD. It is possible that these disorders show disease-specific tau

phosphorylation, or that tau is processed or truncated in a way that is not recognised by available assays. Another potential explanation for the apparent AD specificity of CSF P-tau is if the amount of pathology were simply greater in AD than in other tauopathies (although there is to the best of our knowledge no published data addressing this hypothesis).

Determining the relative specificity of P-tau elevation and AD has considerable advantages in differentiating different neurodegenerative diseases. For example, the ratio of T-tau to P-tau is a quite specific test for CJD (Riemenschneider et al., 2003; Skillback et al., 2014b). There are at present only three conditions in addition to AD in which elevated CSF P-tau levels have been reported: (i) term and pre-term newborns, possibly reflecting physiological tau phosphorylation in brain development (Mattsson et al., 2009b), (ii) herpes encephalitis (Grahn et al., 2013), and (iii) superficial CNS siderosis (Kondziella and Zetterberg, 2008; Ikeda et al., 2010). For obvious reasons, these conditions are not often considered as differential diagnoses for AD. Nevertheless, they may shed light on mechanisms behind CSF P-tau increase, as may emerging data on tau phosphorylation in hibernating squirrels (Williams et al., 2012) and hamsters (Hartig et al., 2007), as well as in anaesthesia (Whittington et al., 2013), pointing to physiological and pathological conditions in which tau phosphorylation occurs potentially as a consequence of reduced neuronal activity.

Diagnostic performance of combined CSF T-tau, P-tau and Aβ42 tests

Multiple studies have investigated the diagnostic accuracy of combined CSF tests for T-tau, P-tau and Aβ42 (Blennow et al., 2010). These studies collectively suggest that in cross-sectional studies aiming to distinguish AD from controls and in longitudinal studies aiming to determine which MCI patients who will develop AD a combined test outperforms each biomarker used alone (Blennow et al., 2010). Higher diagnostic performance is typically seen in single-centre studies (Johansson et al., 2011; Hansson et al., 2006), whereas large multi-centre studies tend to report slightly lower sensitivities and specificities (Mattsson et al., 2009c; Visser et al., 2009). The association of elevated T-tau and P-tau and reduced Aβ42 with AD neuropathology has been validated in autopsy (Shaw et al., 2009) and brain biopsy (Seppala et al., 2012) studies. The influence of AD phenotype on CSF biomarkers has been less thoroughly explored in clinical variants of AD, including AD presenting with the logopenic variant of primary progressive aphasia (Bibl et al., 2011) or a corticobasal syndrome (Borroni et al., 2011).

Longitudinal changes in CSF AD biomarkers

Recent data show that it is possible to identify longitudinal changes in CSF Aβ42, T-tau and P-tau in cognitively healthy controls followed over several years (Toledo et al., 2013; Mattsson et al., 2013b; Moghekar et al., 2013), although most studies (with exceptions (Toledo et al., 2013)) show that CSF AD biomarkers are essentially stable once patients have converted to AD (Zetterberg et al., 2007; Blennow et al., 2007; Mattsson et al., 2012a). This biomarker stability (at least during short term follow-up) may be useful in clinical trials to help identify effects of interventions on the intended biological target, such as altered Aβ homeostasis in response to an anti-Aβ treatment. One of the relatively few longitudinal studies of cognitively normal individuals, where repeated lumbar punctures were performed, suggests that Aβ42 and tau changes occur in parallel and predict incident cognitive symptoms better than absolute baseline levels (Moghekar et al., 2013). CSF measurements may track trajectories of specific Aβ and APP metabolites (Mattsson et al., 2012b; Lannfelt et al., 2008; May et al., 2011; Portelius et al., 2010), as well as down-stream effects, such as reduced axonal degeneration in response to a disease-modifying drug (Gilman et al., 2005; Blennow et al., 2012).

CSF markers of synapse loss

Recently, several independent studies have shown that the CSF concentration of the dendritic protein neurogranin (Ng) is increased in AD (Thorsell et al., 2010; Kvartsberg et al., 2015a; Kvartsberg et al., 2015b; Hellwig et al., 2015; Kester et al., 2015), but not in other neurodegenerative disorders (Wellington et al., 2016), and that the marker predicts future cognitive decline, brain atrophy and reduction in glucose metabolism in prodromal disease stages (Portelius et al., 2015; Tarawneh et al., 2016). Currently, CSF Ng is the best established CSF biomarker for synapse loss in AD, although there are other promising markers, including SNAP-25, in development (Brinkmalm et al., 2014).

CSF markers of microglial activation

AD is tightly linked to activation of the inflammatory M1 phenotype of microglia, the resident macrophages of the brain. Chitotriosidase is an enzyme that is secreted by activated macrophages (Renkema et al., 1998) and its plasma levels are increased in patients with the lysosomal storage disorder Gaucher's disease (Hollak et al., 1994). Increased CSF chitotriosidase activity has been found in AD patients compared with non-demented controls

(Watabe-Rudolph et al., 2012; Mattsson et al., 2011b). A glycoprotein that has great homology with chitotriosidase but lacks its enzymatic activity is YKL-40 (Hakala et al., 1993). YKL-40 is expressed in both microglia and astrocytes and elevated levels have been reported in both prodromal AD and cerebrovascular disease (Craig-Schapiro et al., 2010; Olsson et al., 2013). Another microglial marker, the C-C chemokine receptor 2, is expressed on monocytes and one of its ligands, C-C chemokine ligand 2 (CCL2), that can be produced by microglia is important for the recruitment of monocytes in the CNS (Sokolova et al., 2009). Higher CSF CCL2 levels have been associated with a faster cognitive decline in MCI patients who developed AD (Westin et al., 2012). CCL2 levels in CSF were increased in AD patients compared with healthy controls (Correa et al., 2011; Galimberti et al., 2006b), as well as in the MCI stage of the disease (Galimberti et al., 2006a). However, one study failed to report any significant differences between AD patients and controls (Mattsson et al., 2011b). Another study found elevated CSF CCL2 levels in AD patients compared with controls, but there was an age-dependent increase in the biomarker level that may have affected the result (Blasko et al., 2006). Moreover, one study reported elevated levels of a soluble form of CD14 in the CSF from AD and PD patients compared with healthy controls (Yin et al., 2009). CD14 is a surface protein, mainly expressed by macrophages. As a cofactor for toll-like receptors, CD14 is essential for the recognition of pathogens by the innate immune system of the brain. Another microglial biomarker that has been detected in CSF of AD patients is neopterin, a degradation product deriving from the purine nucleotide guanosine triphosphate. However, no significant differences between AD and controls have been seen to date (Engelborghs et al., 1999). Finally, recent reports suggest that the CSF concentration of the secreted ectodomain of triggering receptor expressed on myeloid cells 2 (Trem2), a molecule that is selectively expressed by microglia in the CNS (Takahashi et al., 2005; Lue et al., 2015) and genetically linked to AD (Jonsson et al., 2013; Guerreiro et al., 2013), is increased in AD in a disease-specific manner and correlates with injury markers in the form of CSF T-tau and P-tau (Heslegrave et al., 2016; Piccio et al., 2016; Suarez-Calvet et al., 2016).

CSF biomarkers for Vascular Dementia

Key molecular pathways involved

Vascular dementia (VaD), sometimes more broadly referred to as vascular cognitive impairment (VCI), is a heterogeneous disease that is due to a variety of cerebrovascular

causes (Rosenberg et al., 2014). Pathological studies have shown that both large and small vessel damage occurs in VaD patients (Gold et al., 2007; Schneider et al., 2007). Large vessel disease leads to strokes with a step-wise course as a result of multiple infarctions that result in concomitant loss of intellect, but is a relatively rare cause of dementia. Much more common is small vessel disease which has several forms: it may either produce lacunes mainly in the basal ganglia without white matter damage or extensive changes in the white matter with or without lacunes. The term subcortical ischemic vascular disease is often used for both lacunar state and white matter disease, but there may be different pathophysiologies involved, particularly when there is cerebral hypoperfusion, which has a major impact on the vulnerable deep white matter (Rosenberg et al., 2014). Diagnosis of cerebrovascular disease has been revolutionised by the advent of neuroimaging, and MRI in particular. Cerebrovascular disease and chronic low-grade hypoxia seem to induce blood-brain barrier (BBB) impairment, extracellular matrix-remodelling and demyelination, which may be reflected in the CSF.

CSF markers of BBB impairment

The best-established fluid biomarker for BBB impairment is the CSF to serum albumin ratio. This marker has been most extensively studied and provides the strongest evidence of a disruption of the BBB in VaD (Wallin et al., 1990), although is not widely used in clinical practice.

CSF markers of tissue-remodelling

Elevated levels of matrix metalloproteinase 9 (MMP-9) in CSF have been shown in patients with VCI and mixed AD/VCI, but not in AD (Adair et al., 2004). Furthermore, tissue inhibitor of metalloproteinase-1 (TIMP-1), a regulator of the MMP system, has also been found to be elevated in CSF; the TIMP-1 CSF concentration has been shown to be correlated to the albumin ratio, possibly reflecting an overall regulation of different MMPs that might be involved in the BBB opening (Bjerke et al., 2011).

CSF markers of white matter injury

CSF markers of white matter injury include myelin basic protein, a protein component of myelin, sulfatide, a class of sulfolipids found in the myelin sheath, and neurofilament light (NFL), which is an axonal protein that is highly expressed in large calibre myelinated axons. All these markers are elevated in VaD and subcortical vascular impairment (Bjerke et al., 2009; Bjerke et al., 2011; Skillback et al., 2014a; Sjogren et al., 2001a; Tullberg et al., 2002;

Tullberg et al., 2000), but not in any disease-specific manner; similar changes are found in other CNS diseases that involve white matter, *e.g.*, multiple sclerosis (Haghighi et al., 2013; Burman et al., 2014).

Dementia with Lewy bodies

Key molecular pathways involved

α-Synuclein-containing, intra-neuronal Lewy bodies are the defining pathological hallmark of DLB, but most patients also have some degree of AD pathology, in particular amyloid plaques (Howlett et al., 2015). Their clinical impact is not known in detail, but there is some evidence from post-mortem studies that such AD changes (plaque and tangle pathology) lead to a more rapid cognitive decline in DLB (Kraybill et al., 2005).

CSF α-synuclein

α-Synuclein is the major component of intra-neuronal Lewy bodies, which are characteristic of Parkinson's disease (PD) and DLB (Mollenhauer et al., 2010). In PD and other synucleinopathies CSF α-synuclein levels are typically reduced (Hall et al., 2012; Mollenhauer et al., 2011), whilst in AD and CJD, the levels are elevated and correlate with T-tau, suggesting that in this context at least α-synuclein may also be an non-specific marker of neurodegeneration (Mollenhauer et al., 2011; Tateno et al., 2012; Wennstrom et al., 2013; Ohrfelt et al., 2009; Slaets et al., 2014). This has been reported not only in AD and CJD, but also in DLB, where there may be a competition between aggregation of α-synuclein into Lewy bodies and release of the protein from degenerating synapses, making the data hard to interpret (Kapaki et al., 2013). Importantly, α-synuclein is highly expressed in red blood cells, a reason why blood contamination during sample collection may further limit any diagnostic value (Barbour et al., 2008; Hong et al., 2010). Currently available assays for α-synuclein measure total amounts of the protein and not Lewy body-specific isoforms; sensitive and specific assays for the latter would resolve this issue.

CSF AD biomarkers in DLB

AD pathology is reflected in the CSF as increased concentrations of T-tau and P-tau and reduced concentration of Aβ42 (Ahmed et al., 2014). High CSF T-tau and T-tau and low CSF

Aβ42 concentrations are seen in 47% of DLB patients (Schoonenboom et al., 2012). This AD biomarker signature has also been demonstrated in PDD (Buongiorno et al., 2011), and low CSF Aβ42 concentration has been found to predict future cognitive decline in PD (Siderowf et al., 2010). AD CSF biomarkers have been linked to earlier death in DLB (Brunnstrom et al., 2013), but their relationship with longitudinal cognitive decline in patients with DLB remains to be examined.

Frontotemporal dementia

Key molecular pathways involved

FTD is a clinically, genetically and pathologically heterogeneous neurodegenerative disorder that preferentially affects the frontal and anterior temporal lobes of the brain. FTD usually presents with behavioural disturbance (behavioural variant FTD, bvFTD) or language impairment (primary progressive aphasia, PPA) but there is also overlap with motor neurone disease (MND) and the atypical parkinsonian disorders, corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP) (Warren et al., 2013). Pathologically, neuronal inclusions are usually found containing abnormal forms of one of two proteins, tau or TDP-43, although less commonly patients may have inclusions containing FUS protein. Around a third of cases are inherited in an autosomal dominant fashion, caused by mutations in progranulin (*GRN*), microtubule-associated protein tau (*MAPT*) or *C9orf72* (Rohrer et al., 2015), and in these cases the pathology can reliably be determined during life (TDP-43 in GRN and C9orf72, tau in MAPT). Whilst there is a fairly good correlation between clinical syndrome and underlying pathology in some sporadic cases, *e.g.*, semantic variant PPA (svPPA) and TDP-43, for the majority of bvFTD and nonfluent variant PPA (nfvPPA) cases there is poor phenotype/pathological correlation.

CSF NFL

Neurofilament biomarker candidates, *i.e.*, neurofilament light chain (NFL) and phosphorylated neurofilament heavy chain (pNFH), are important proteins of the axonal cytoskeleton. In FTD, CSF NFL has been shown to be higher compared with AD (de Jong et al., 2007; Landqvist Waldo et al., 2013; Sjogren et al., 2000); a result that was recently confirmed in a large retrospective analysis of data from the Swedish Dementia Registry (Skillback et al., 2014a).

CSF TDP-43

The presence of aggregates positive for the TAR DNA-binding protein of 43 kDa (TDP-43) accounts for about 50% of FTD patients and is found in FTD-MND, in most svPPA patients and only seldom in nfvPPA or CBS. TDP-43 can be measured in CSF but, unfortunately, most of the protein appears to be blood-derived and its CSF concentration does not reflect neuropathology and is unaltered in FTD (Feneberg et al., 2014; Steinacker et al., 2008).

CSF progranulin

Progranulin concentration has been shown to be reduced in CSF and plasma in progranulin (*GRN*) mutation carriers but not in other FTD cases (Ghidoni et al., 2008). This was confirmed recently by several studies (Morenas-Rodriguez et al., 2016) and suggests progranulin determination as an alternative to genetic testing for the identification of *GRN* mutation carriers.

CSF AD biomarkers

BvFTD is the neurodegenerative disease with the smallest proportion of AD biomarker-positive cases (Skillback et al., 2015). Combining the classical AD biomarkers (CSF T-tau, P-tau and Aβ42, all normal) with NFL (increased) results in diagnostic sensitivities of 75-86% and specificities of 94-100% for FTD as compared to AD and cognitively normal controls (de Jong et al., 2007).

Standardization efforts

The clinical utility of CSF tests for T-tau, P-tau and Aβ42 is clear and their importance for selecting patients in pre-dementia stages of AD for clinical trials of disease-modifying drug candidates is undisputed (Lleo et al., 2015). However, most of the commercially available assays for these biomarkers are still research-grade, and there is a lack of common calibrators or certified reference measurement systems that can be used for standardisation (Mattsson et al., 2012c). This leads to a risk of bias in the biomarker measurements across different assay platforms. A recognisable consequence of this is that optimal CSF Aβ42 cut-points for differentiating AD patients from control individuals vary from 192 ng/L (Shaw et al., 2009) to around 550 ng/L (Hansson et al., 2006; Duits et al., 2014) or even higher (Palmqvist et al., 2014), depending on the assay format and reference standard for diagnosis used. The

development of certified reference methods and materials for CSF T-tau, P-tau and Aβ42, led by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Working Group on CSF Proteins, will at least partly solve this issue. This work has come the furthest for CSF Aβ42 for which two mass spectrometry-based reference methods have been published and formally certified by the Joint Committee for Traceability in Laboratory Medicine (JCTLM; database identification numbers C11RMP9 and C12RMP1, respectively) (Korecka et al., 2014; Leinenbach et al., 2014). A CSF-based reference material for CSF Aβ42 is currently under evaluation (Bjerke et al., 2015).

Another issue is random variation in the biomarker measurements, even when the same assay is used. This can be seen in multi-centre comparisons of measurements, including the Alzheimer's Association QC Program for CSF Biomarkers (Mattsson et al., 2011a; Mattsson et al., 2013a). This program includes around 90 participants around the globe and shows that the inter-laboratory coefficients of variation (CVs) for commercially available tau and Aβ assays are between 20-30%, whereas intra-laboratory studies show that CVs of <10% should be feasible. Recent advancements in the development of fully automated assays have resulted in inter-laboratory CVs of 1-4% in the Alzheimer's Association QC Programme, thus showing promise for the future (Bittner et al., 2015).

Important pre-analytical sources of variation for the most variable AD biomarker, Aβ42, are storage tube type (polypropylene tubes are recommended but different brands seem to show different analyte adsorption (Perret-Liaudet et al., 2012)); sample aliquot volume (Toombs et al., 2013); the number of tube transfers of the collected CSF (Toombs et al., 2014); and blood contamination (Bjerke et al., 2010). Analytical sources of variation include the composition of the diluent buffer – low concentrations of detergent increase the measured Aβ42 concentration, which has to be standardised (Bjerke et al., 2010). Several additional factors may be important in an assay-specific manner and close adherence to kit inserts is recommended, as is participation in the Alzheimer's Association QC programme and other inter-laboratory comparison programmes to ensure that proper laboratory procedures are in place.

CSF biomarker-supported diagnostic criteria

Patients with AD are routinely diagnosed by clinical criteria, commonly the international classification of diseases (ICD10) or NINCDS-ADRDA criteria (McKhann et al., 1984). However, the "gold standard" diagnostic method for AD is to perform an autopsy to find neuropathological AD changes (neuronal loss along with plaque and tangle pathology) at a sufficient degree to confer a diagnosis (Mirra et al., 1991). The recently published updated diagnostic criteria from the International Working Group (IWG-2) for New Research Criteria for the Diagnosis of AD propose that AD can be diagnosed when the specific clinical phenotype of episodic memory impairment is present together with low levels of CSF Aβ42 and high levels of either T-tau or P-tau (Dubois et al., 2014). Additionally, these new criteria also recognise "atypical" AD, the latter comprising posterior (visual or biparietal), logopenic (language) and frontal (behavioural) clinical variants, if there is also biomarker evidence of AD pathology (Dubois et al., 2014). Biomarker-supported criteria have also been proposed by the US National Institute on Aging (NIA) allowing for a diagnosis of preclinical AD, MCI due to AD and dementia due to Alzheimer's disease. For VaD, DLB and FTD, no biomarkers accurate enough to be included in clinical criteria have been presented as of to date.

Concluding remarks

Three CSF biomarkers reflecting the core pathological features of AD are in common use: T-tau (broadly, but not entirely reflecting neurodegeneration), P-tau (reflecting tau hyperphosphorylation and tangle formation) and Aβ42 (which inversely correlates with plaque pathology). According to revised clinical criteria, these markers may help diagnose AD more accurately and open up the possibility of detecting pre-dementia stages of the disease (Dubois et al., 2014). At present, their most obvious utility is in clinical trials of novel disease-modifying treatments against AD. In the future, they may help selecting the right treatment for individual patients by making it possible to assess which molecular pathology that is most likely to cause the patient's symptoms at different stages of the disease. In addition, there is considerable promise that CSF biomarkers will be able to provide in *vivo* measurement of a range of additional pathophysiological processes in AD, including microglial activation and synapse loss. In regards to other neurodegenerative disorders, CSF NFL is a promising marker to detect degeneration of large calibre axons in VaD and FTD. Specific CSF markers for TDP-43, Lewy bodies and other protein inclusions (e.g., FUS and dipeptide repeats) are urgently needed.

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References

Adair JC, Charlie J, Dencoff JE, et al. (2004). Measurement of gelatinase B (MMP-9) in the cerebrospinal fluid of patients with vascular dementia and Alzheimer disease. Stroke 35: e159-162.

Ahmed RM, Paterson RW, Warren JD, et al. (2014). Biomarkers in dementia: clinical utility and new directions. J Neurol Neurosurg Psychiatry 85: 1426-1434.

Andreasen N, Minthon L, Vanmechelen E, et al. (1999). Cerebrospinal fluid tau and Abeta42 as predictors of development of Alzheimer's disease in patients with mild cognitive impairment. Neurosci Lett 273: 5-8.

Barbour R, Kling K, Anderson JP, et al. (2008). Red blood cells are the major source of alpha-synuclein in blood. Neurodegener Dis 5: 55-59.

Bibl M, Mollenhauer B, Lewczuk P, et al. (2011). Cerebrospinal fluid tau, p-tau 181 and amyloid-beta38/40/42 in frontotemporal dementias and primary progressive aphasias. Dement Geriatr Cogn Disord 31: 37-44.

Bittner T, Zetterberg H, Teunissen CE, et al. (2015). Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of beta-amyloid (1-42) in human cerebrospinal fluid. Alzheimers Dement.

Bjerke M, Andreasson U, Kuhlmann J, et al. (2015). Assessing the commutability of reference material formats for the harmonization of amyloid beta measurements. Clin Chem Lab Med.

Bjerke M, Andreasson U, Rolstad S, et al. (2009). Subcortical vascular dementia biomarker pattern in mild cognitive impairment. Dement Geriatr Cogn Disord 28: 348-356.

Bjerke M, Portelius E, Minthon L, et al. (2010). Confounding factors influencing amyloid Beta concentration in cerebrospinal fluid. Int J Alzheimers Dis 2010.

Bjerke M, Zetterberg H, Edman A, et al. (2011). Cerebrospinal fluid matrix metalloproteinases and tissue inhibitor of metalloproteinases in combination with subcortical and cortical biomarkers in vascular dementia and Alzheimer's disease. J Alzheimers Dis 27: 665-676.

Blasko I, Lederer W, Oberbauer H, et al. (2006). Measurement of thirteen biological markers in CSF of patients with Alzheimer's disease and other dementias. Dement Geriatr Cogn Disord 21: 9-15.

Blennow K, de Leon MJ & Zetterberg H (2006). Alzheimer's disease. Lancet 368: 387-403.

Blennow K, Hampel H, Weiner M, et al. (2010). Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. Nat Rev Neurol 6: 131-144.

Blennow K, Wallin A, Agren H, et al. (1995). Tau protein in cerebrospinal fluid: a biochemical marker for axonal degeneration in Alzheimer disease? Mol Chem Neuropathol 26: 231-245.

Blennow K, Zetterberg H, Minthon L, et al. (2007). Longitudinal stability of CSF biomarkers in Alzheimer's disease. Neurosci Lett 419: 18-22.

Blennow K, Zetterberg H, Rinne JO, et al. (2012). Effect of immunotherapy with bapineuzumab on cerebrospinal fluid biomarker levels in patients with mild to moderate Alzheimer disease. Arch Neurol 69: 1002-1010.
Borroni B, Premi E, Agosti C, et al. (2011). CSF Alzheimer's disease-like pattern in corticobasal syndrome: evidence for a distinct disorder. J Neurol Neurosurg Psychiatry 82: 834-838.
Brinkmalm A, Brinkmalm G, Honer WG, et al. (2014). SNAP-25 is a promising novel cerebrospinal fluid biomarker for synapse degeneration in Alzheimer's disease. Mol Neurodegener 9: 53.
Brunnstrom H, Hansson O, Zetterberg H, et al. (2013). Correlations of CSF tau and amyloid levels with Alzheimer pathology in neuropathologically verified dementia with Lewy bodies. Int J Geriatr Psychiatry 28: 738-744.
Buchhave P, Minthon L, Zetterberg H, et al. (2012). Cerebrospinal Fluid Levels of beta-Amyloid 1-42, but Not of Tau, Are Fully Changed Already 5 to 10 Years Before the Onset of Alzheimer Dementia. Arch Gen Psychiatry 69: 98-106.
Buerger K, Ewers M, Pirttila T, et al. (2006). CSF phosphorylated tau protein correlates with neocortical neurofibrillary pathology in Alzheimer's disease. Brain 129: 3035-3041.
Buongiorno M, Compta Y & Marti MJ (2011). Amyloid-beta and tau biomarkers in Parkinson's disease-dementia. J Neurol Sci 310: 25-30.
Burman J, Zetterberg H, Fransson M, et al. (2014). Assessing tissue damage in multiple sclerosis: a biomarker approach. Acta Neurol Scand 130: 81-89.
Correa JD, Starling D, Teixeira AL, et al. (2011). Chemokines in CSF of Alzheimer's disease patients. Arq Neuropsiquiatr 69: 455-459.
Craig-Schapiro R, Perrin RJ, Roe CM, et al. (2010). YKL-40: a novel prognostic fluid biomarker for preclinical Alzheimer's disease. Biol Psychiatry 68: 903-912.
de Jong D, Jansen RW, Pijnenburg YA, et al. (2007). CSF neurofilament proteins in the differential diagnosis of dementia. J Neurol Neurosurg Psychiatry 78: 936-938.
Dubois B, Feldman HH, Jacova C, et al. (2014). Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 13: 614-629.
Duits FH, Teunissen CE, Bouwman FH, et al. (2014). The cerebrospinal fluid "Alzheimer profile": Easily said, but what does it mean? Alzheimers Dement.
Engelborghs S, De Brabander M, De Cree J, et al. (1999). Unchanged levels of interleukins, neopterin, interferon-gamma and tumor necrosis factor-alpha in cerebrospinal fluid of patients with dementia of the Alzheimer type. Neurochem Int 34: 523-530.
Fagan AM, Head D, Shah AR, et al. (2009). Decreased cerebrospinal fluid Abeta(42) correlates with brain atrophy in cognitively normal elderly. Ann Neurol 65: 176-183.
Fagan AM, Mintun MA, Mach RH, et al. (2006). Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta42 in humans. Ann Neurol 59: 512-519.
Feneberg E, Steinacker P, Lehnert S, et al. (2014). Limited role of free TDP-43 as a diagnostic tool in neurodegenerative diseases. Amyotroph Lateral Scler Frontotemporal Degener 15: 351-356.
Forsberg A, Engler H, Almkvist O, et al. (2008). PET imaging of amyloid deposition in patients with mild cognitive impairment. Neurobiol Aging 29: 1456-1465.
Galimberti D, Schoonenboom N, Scheltens P, et al. (2006a). Intrathecal chemokine synthesis in mild cognitive impairment and Alzheimer disease. Arch Neurol 63: 538-543.
Galimberti D, Schoonenboom N, Scheltens P, et al. (2006b). Intrathecal chemokine levels in Alzheimer disease and frontotemporal lobar degeneration. Neurology 66: 146-147.
Ghidoni R, Benussi L, Glionna M, et al. (2008). Low plasma progranulin levels predict progranulin mutations in frontotemporal lobar degeneration. Neurology 71: 1235-1239.

Gilman S, Koller M, Black RS, et al. (2005). Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. Neurology 64: 1553-1562.
Gisslen M, Krut J, Andreasson U, et al. (2009). Amyloid and tau cerebrospinal fluid biomarkers in HIV infection. BMC Neurol 9: 63.
Glodzik L, Mosconi L, Tsui W, et al. (2012). Alzheimer's disease markers, hypertension, and gray matter damage in normal elderly. Neurobiol Aging 33: 1215-1227.
Gold G, Giannakopoulos P, Herrmann FR, et al. (2007). Identification of Alzheimer and vascular lesion thresholds for mixed dementia. Brain 130: 2830-2836.
Grahn A, Hagberg L, Nilsson S, et al. (2013). Cerebrospinal fluid biomarkers in patients with varicella-zoster virus CNS infections. J Neurol 260: 1813-1821.
Guerreiro R, Wojtas A, Bras J, et al. (2013). TREM2 variants in Alzheimer's disease. N Engl J Med 368: 117-127.
Gustafson DR, Skoog I, Rosengren L, et al. (2007). Cerebrospinal fluid beta-amyloid 1-42 concentration may predict cognitive decline in older women. J Neurol Neurosurg Psychiatry 78: 461-464.
Haass C, Schlossmacher MG, Hung AY, et al. (1992). Amyloid beta-peptide is produced by cultured cells during normal metabolism. Nature 359: 322-325.
Haghighi S, Lekman A, Nilsson S, et al. (2013). Increased CSF sulfatide levels and serum glycosphingolipid antibody levels in healthy siblings of multiple sclerosis patients. J Neurol Sci 326: 35-39.
Hakala BE, White C & Recklies AD (1993). Human cartilage gp-39, a major secretory product of articular chondrocytes and synovial cells, is a mammalian member of a chitinase protein family. J Biol Chem 268: 25803-25810.
Hall S, Ohrfelt A, Constantinescu R, et al. (2012). Accuracy of a Panel of 5 Cerebrospinal Fluid Biomarkers in the Differential Diagnosis of Patients With Dementia and/or Parkinsonian Disorders. Arch Neurol: 1-8.
Hampel H, Buerger K, Zinkowski R, et al. (2004). Measurement of phosphorylated tau epitopes in the differential diagnosis of Alzheimer disease: a comparative cerebrospinal fluid study. Arch Gen Psychiatry 61: 95-102.
Hansson O, Zetterberg H, Buchhave P, et al. (2006). Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. Lancet Neurol 5: 228-234.
Hartig W, Stieler J, Boerema AS, et al. (2007). Hibernation model of tau phosphorylation in hamsters: selective vulnerability of cholinergic basal forebrain neurons - implications for Alzheimer's disease. Eur J Neurosci 25: 69-80.
Hellwig K, Kvartsberg H, Portelius E, et al. (2015). Neurogranin and YKL-40: independent markers of synaptic degeneration and neuroinflammation in Alzheimer's disease. Alzheimers Res Ther 7: 74.
Heslegrave A, Heywood W, Paterson R, et al. (2016). Increased cerebrospinal fluid soluble TREM2 concentration in Alzheimer's disease. Mol Neurodegener 11: 3.
Hesse C, Rosengren L, Andreasen N, et al. (2001). Transient increase in total tau but not phospho-tau in human cerebrospinal fluid after acute stroke. Neurosci Lett 297: 187-190.
Hollak CE, van Weely S, van Oers MH, et al. (1994). Marked elevation of plasma chitotriosidase activity. A novel hallmark of Gaucher disease. J Clin Invest 93: 1288-1292.
Hong Z, Shi M, Chung KA, et al. (2010). DJ-1 and alpha-synuclein in human cerebrospinal fluid as biomarkers of Parkinson's disease. Brain 133: 713-726.

Howlett DR, Whitfield D, Johnson M, et al. (2015). Regional Multiple Pathology Scores Are Associated with Cognitive Decline in Lewy Body Dementias. Brain Pathol 25: 401-408.
Ikeda T, Noto D, Noguchi-Shinohara M, et al. (2010). CSF tau protein is a useful marker for effective treatment of superficial siderosis of the central nervous system: two case reports. Clin Neurol Neurosurg 112: 62-64.
Jellinger KA & Attems J (2015). Challenges of multimorbidity of the aging brain: a critical update. J Neural Transm (Vienna) 122: 505-521.
Johansson P, Mattsson N, Hansson O, et al. (2011). Cerebrospinal fluid biomarkers for Alzheimer's disease: diagnostic performance in a homogeneous mono-center population. J Alzheimers Dis 24: 537-546.
Jonsson T, Stefansson H, Steinberg S, et al. (2013). Variant of TREM2 associated with the risk of Alzheimer's disease. N Engl J Med 368: 107-116.
Kapaki E, Paraskevas GP, Emmanouilidou E, et al. (2013). The diagnostic value of CSF alpha-synuclein in the differential diagnosis of dementia with Lewy bodies vs. normal subjects and patients with Alzheimer's disease. PLoS ONE 8: e81654.
Kester MI, Teunissen CE, Crimmins DL, et al. (2015). Neurogranin as a Cerebrospinal Fluid Biomarker for Synaptic Loss in Symptomatic Alzheimer Disease. JAMA Neurol 72: 1275-1280.
Kondziella D & Zetterberg H (2008). Hyperphosphorylation of tau protein in superficial CNS siderosis. J Neurol Sci 273: 130-132.
Korecka M, Waligorska T, Figurski M, et al. (2014). Qualification of a surrogate matrix-based absolute quantification method for amyloid-beta(4)(2) in human cerebrospinal fluid using 2D UPLC-tandem mass spectrometry. J Alzheimers Dis 41: 441-451.
Kraybill ML, Larson EB, Tsuang DW, et al. (2005). Cognitive differences in dementia patients with autopsy-verified AD, Lewy body pathology, or both. Neurology 64: 2069-2073.
Kvartsberg H, Duits FH, Ingelsson M, et al. (2015a). Cerebrospinal fluid levels of the synaptic protein neurogranin correlates with cognitive decline in prodromal Alzheimer's disease. Alzheimers Dement 11: 1180-1190.
Kvartsberg H, Portelius E, Andreasson U, et al. (2015b). Characterization of the postsynaptic protein neurogranin in paired cerebrospinal fluid and plasma samples from Alzheimer's disease patients and healthy controls. Alzheimers Res Ther 7: 40.
Landqvist Waldo M, Frizell Santillo A, Passant U, et al. (2013). Cerebrospinal fluid neurofilament light chain protein levels in subtypes of frontotemporal dementia. BMC Neurol 13: 54.
Lannfelt L, Blennow K, Zetterberg H, et al. (2008). Safety, efficacy, and biomarker findings of PBT2 in targeting Abeta as a modifying therapy for Alzheimer's disease: a phase IIa, double-blind, randomised, placebo-controlled trial. Lancet Neurol 7: 779-786.
Leinenbach A, Pannee J, Dulffer T, et al. (2014). Mass Spectrometry-Based Candidate Reference Measurement Procedure for Quantification of Amyloid-beta in Cerebrospinal Fluid. Clin Chem.
Lleo A, Cavedo E, Parnetti L, et al. (2015). Cerebrospinal fluid biomarkers in trials for Alzheimer and Parkinson diseases. Nat Rev Neurol 11: 41-55.
Lue LF, Schmitz CT, Serrano G, et al. (2015). TREM2 Protein Expression Changes Correlate with Alzheimer's Disease Neurodegenerative Pathologies in Post-Mortem Temporal Cortices. Brain Pathol 25: 469-480.
Maia LF, Kaeser SA, Reichwald J, et al. (2013). Changes in Amyloid-beta and Tau in the Cerebrospinal Fluid of Transgenic Mice Overexpressing Amyloid Precursor Protein. Sci Transl Med 5: 194re192.

Masters CL, Simms G, Weinman NA, et al. (1985). Amyloid plaque core protein in Alzheimer disease and Down syndrome. Proc Natl Acad Sci U S A 82: 4245-4249.
Mattsson N, Andreasson U, Persson S, et al. (2011a). The Alzheimer's Association external quality control program for cerebrospinal fluid biomarkers. Alzheimers Dement 7: 386-395 e386.
Mattsson N, Andreasson U, Persson S, et al. (2013a). CSF biomarker variability in the Alzheimer's Association quality control program. Alzheimers Dement 9: 251-261.
Mattsson N, Axelsson M, Haghighi S, et al. (2009a). Reduced cerebrospinal fluid BACE1 activity in multiple sclerosis. Mult Scler.
Mattsson N, Bremell D, Anckarsater R, et al. (2010). Neuroinflammation in Lyme neuroborreliosis affects amyloid metabolism. BMC Neurol 10: 51.
Mattsson N, Insel P, Nosheny R, et al. (2013b). CSF protein biomarkers predicting longitudinal reduction of CSF beta-amyloid42 in cognitively healthy elders. Transl Psychiatry 3: e293.
Mattsson N, Portelius E, Rolstad S, et al. (2012a). Longitudinal cerebrospinal fluid biomarkers over four years in mild cognitive impairment. J Alzheimers Dis 30: 767-778.
Mattsson N, Rajendran L, Zetterberg H, et al. (2012b). BACE1 inhibition induces a specific cerebrospinal fluid beta-amyloid pattern that identifies drug effects in the central nervous system. PLoS ONE 7: e31084.
Mattsson N, Savman K, Osterlundh G, et al. (2009b). Converging molecular pathways in human neural development and degeneration. Neurosci Res.
Mattsson N, Tabatabaei S, Johansson P, et al. (2011b). Cerebrospinal fluid microglial markers in Alzheimer's disease: elevated chitotriosidase activity but lack of diagnostic utility. Neuromolecular Med 13: 151-159.
Mattsson N, Zegers I, Andreasson U, et al. (2012c). Reference measurement procedures for Alzheimer's disease cerebrospinal fluid biomarkers: definitions and approaches with focus on amyloid beta42. Biomark Med 6: 409-417.
Mattsson N, Zetterberg H, Hansson O, et al. (2009c). CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. Jama 302: 385-393.
May PC, Dean RA, Lowe SL, et al. (2011). Robust central reduction of amyloid-beta in humans with an orally available, non-peptidic beta-secretase inhibitor. J Neurosci 31: 16507-16516.
McKhann G, Drachman D, Folstein M, et al. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34: 939-944.
Meredith JE, Jr., Sankaranarayanan S, Guss V, et al. (2013). Characterization of Novel CSF Tau and ptau Biomarkers for Alzheimer's Disease. PLoS ONE 8: e76523.
Mirra SS, Heyman A, McKeel D, et al. (1991). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 41: 479-486.
Moghekar A, Li S, Lu Y, et al. (2013). CSF biomarker changes precede symptom onset of mild cognitive impairment. Neurology.
Mollenhauer B, El-Agnaf OM, Marcus K, et al. (2010). Quantification of alpha-synuclein in cerebrospinal fluid as a biomarker candidate: review of the literature and considerations for future studies. Biomark Med 4: 683-699.
Mollenhauer B, Locascio JJ, Schulz-Schaeffer W, et al. (2011). alpha-Synuclein and tau concentrations in cerebrospinal fluid of patients presenting with parkinsonism: a cohort study. Lancet Neurol 10: 230-240.

Morenas-Rodriguez E, Cervera-Carles L, Vilaplana E, et al. (2016). Progranulin Protein Levels in Cerebrospinal Fluid in Primary Neurodegenerative Dementias. Journal of Alzheimers Disease 50: 539-546.
Motter R, Vigo-Pelfrey C, Kholodenko D, et al. (1995). Reduction of beta-amyloid peptide42 in the cerebrospinal fluid of patients with Alzheimer's disease. Ann Neurol 38: 643-648.
Ohrfelt A, Grognet P, Andreasen N, et al. (2009). Cerebrospinal fluid alpha-synuclein in neurodegenerative disorders-a marker of synapse loss? Neurosci Lett 450: 332-335.
Olsson B, Hertze J, Lautner R, et al. (2013). Microglial markers are elevated in the prodromal phase of Alzheimer's disease and vascular dementia. J Alzheimers Dis 33: 45-53.
Olsson B, Lautner R, Andreasson U, et al. (2016). CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol In press.
Palmqvist S, Zetterberg H, Blennow K, et al. (2014). Accuracy of brain amyloid detection in clinical practice using cerebrospinal fluid beta-amyloid 42: a cross-validation study against amyloid positron emission tomography. JAMA Neurol 71: 1282-1289.
Perret-Liaudet A, Pelpel M, Tholance Y, et al. (2012). Risk of Alzheimer's disease biological misdiagnosis linked to cerebrospinal collection tubes. J Alzheimers Dis 31: 13-20.
Piccio L, Deming Y, Del-Aguila JL, et al. (2016). Cerebrospinal fluid soluble TREM2 is higher in Alzheimer disease and associated with mutation status. Acta Neuropathol.
Portelius E, Dean RA, Gustavsson MK, et al. (2010). A novel Abeta isoform pattern in CSF reflects gamma-secretase inhibition in Alzheimer disease. Alzheimers Res Ther 2: 7.
Portelius E, Price E, Brinkmalm G, et al. (2011). A novel pathway for amyloid precursor protein processing. Neurobiol Aging 32: 1090-1098.
Portelius E, Zetterberg H, Skillback T, et al. (2015). Cerebrospinal fluid neurogranin: relation to cognition and neurodegeneration in Alzheimer's disease. Brain 138: 3373-3385.
Renkema GH, Boot RG, Au FL, et al. (1998). Chitotriosidase, a chitinase, and the 39-kDa human cartilage glycoprotein, a chitin-binding lectin, are homologues of family 18 glycosyl hydrolases secreted by human macrophages. Eur J Biochem 251: 504-509.
Riemenschneider M, Wagenpfeil S, Vanderstichele H, et al. (2003). Phospho-tau/total tau ratio in cerebrospinal fluid discriminates Creutzfeldt-Jakob disease from other dementias. Mol Psychiatry 8: 343-347.
Rohrer JD, Nicholas JM, Cash DM, et al. (2015). Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis. Lancet Neurol 14: 253-262.
Rosen C, Hansson O, Blennow K, et al. (2013). Fluid biomarkers in Alzheimer's disease - current concepts. Mol Neurodegener 8: 20.
Rosenberg GA, Bjerke M & Wallin A (2014). Multimodal markers of inflammation in the subcortical ischemic vascular disease type of vascular cognitive impairment. Stroke 45: 1531-1538.
Saman S, Kim W, Raya M, et al. (2012). Exosome-associated tau is secreted in tauopathy models and is selectively phosphorylated in cerebrospinal fluid in early Alzheimer disease. J Biol Chem 287: 3842-3849.
Sanchez-Juan P, Sanchez-Valle R, Green A, et al. (2007). Influence of timing on CSF tests value for Creutzfeldt-Jakob disease diagnosis. J Neurol 254: 901-906.
Schneider JA, Arvanitakis Z, Bang W, et al. (2007). Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 69: 2197-2204.
Schoonenboom NS, Mulder C, Van Kamp GJ, et al. (2005). Amyloid beta 38, 40, and 42 species in cerebrospinal fluid: more of the same? Ann Neurol 58: 139-142.

Schoonenboom NS, Reesink FE, Verwey NA, et al. (2012). Cerebrospinal fluid markers for differential dementia diagnosis in a large memory clinic cohort. Neurology 78: 47-54.
Seppala TT, Nerg O, Koivisto AM, et al. (2012). CSF biomarkers for Alzheimer disease correlate with cortical brain biopsy findings. Neurology 78: 1568-1575.
Shaw LM, Vanderstichele H, Knapik-Czajka M, et al. (2009). Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol 65: 403-413.
Siderowf A, Xie SX, Hurtig H, et al. (2010). CSF amyloid {beta} 1-42 predicts cognitive decline in Parkinson disease. Neurology 75: 1055-1061.
Sjogren M, Blomberg M, Jonsson M, et al. (2001a). Neurofilament protein in cerebrospinal fluid: a marker of white matter changes. J Neurosci Res 66: 510-516.
Sjogren M, Gisslen M, Vanmechelen E, et al. (2001b). Low cerebrospinal fluid beta-amyloid 42 in patients with acute bacterial meningitis and normalization after treatment. Neurosci Lett 314: 33-36.
Sjogren M, Rosengren L, Minthon L, et al. (2000). Cytoskeleton proteins in CSF distinguish frontotemporal dementia from AD. Neurology 54: 1960-1964.
Skillback T, Farahmand B, Bartlett JW, et al. (2014a). CSF neurofilament light differs in neurodegenerative diseases and predicts severity and survival. Neurology 83: 1945-1953.
Skillback T, Farahmand BY, Rosen C, et al. (2015). Cerebrospinal fluid tau and amyloid-beta(1-42) in patients with dementia. Brain 138: 2716-2731.
Skillback T, Rosen C, Asztely F, et al. (2014b). Diagnostic performance of cerebrospinal fluid total tau and phosphorylated tau in Creutzfeldt-Jakob disease: results from the Swedish Mortality Registry. JAMA Neurol 71: 476-483.
Skoog I, Davidsson P, Aevarsson O, et al. (2003). Cerebrospinal fluid beta-amyloid 42 is reduced before the onset of sporadic dementia: a population-based study in 85-year-olds. Dement Geriatr Cogn Disord 15: 169-176.
Slaets S, Vanmechelen E, Le Bastard N, et al. (2014). Increased CSF alpha-synuclein levels in Alzheimer's disease: correlation with tau levels. Alzheimers Dement 10: S290-298.
Sokolova A, Hill MD, Rahimi F, et al. (2009). Monocyte chemoattractant protein-1 plays a dominant role in the chronic inflammation observed in Alzheimer's disease. Brain Pathol 19: 392-398.
Steinacker P, Hendrich C, Sperfeld AD, et al. (2008). TDP-43 in cerebrospinal fluid of patients with frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Arch Neurol 65: 1481-1487.
Strozyk D, Blennow K, White LR, et al. (2003). CSF Abeta 42 levels correlate with amyloid-neuropathology in a population-based autopsy study. Neurology 60: 652-656.
Suarez-Calvet M, Kleinberger G, Araque Caballero MA, et al. (2016). 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.
Takahashi K, Rochford CD & Neumann H (2005). Clearance of apoptotic neurons without inflammation by microglial triggering receptor expressed on myeloid cells-2. J Exp Med 201: 647-657.
Tarawneh R, D'Angelo G, Crimmins D, et al. (2016). Diagnostic and Prognostic Utility of the Synaptic Marker Neurogranin in Alzheimer Disease. JAMA Neurol.
Tateno F, Sakakibara R, Kawai T, et al. (2012). Alpha-synuclein in the cerebrospinal fluid differentiates synucleinopathies (Parkinson Disease, dementia with Lewy bodies, multiple system atrophy) from Alzheimer disease. Alzheimer Dis Assoc Disord 26: 213-216.

Terry RD, Masliah E, Salmon DP, et al. (1991). Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol 30: 572-580.
Thorsell A, Bjerke M, Gobom J, et al. (2010). Neurogranin in cerebrospinal fluid as a marker of synaptic degeneration in Alzheimer's disease. Brain Res 1362: 13-22.
Toledo JB, Xie SX, Trojanowski JQ, et al. (2013). Longitudinal change in CSF Tau and Abeta biomarkers for up to 48 months in ADNI. Acta Neuropathol 126: 659-670.
Toombs J, Paterson RW, Lunn MP, et al. (2013). Identification of an important potential confound in CSF AD studies: aliquot volume. Clin Chem Lab Med: 1-7.
Toombs J, Paterson RW, Schott JM, et al. (2014). Amyloid-beta 42 adsorption following serial tube transfer. Alzheimers Res Ther 6: 5.
Trojanowski JQ, Schuck T, Schmidt ML, et al. (1989). Distribution of tau proteins in the normal human central and peripheral nervous system. J Histochem Cytochem 37: 209-215.
Tullberg M, Hultin L, Ekholm S, et al. (2002). White matter changes in normal pressure hydrocephalus and Binswanger disease: specificity, predictive value and correlations to axonal degeneration and demyelination. Acta Neurol Scand 105: 417-426.
Tullberg M, Mansson JE, Fredman P, et al. (2000). CSF sulfatide distinguishes between normal pressure hydrocephalus and subcortical arteriosclerotic encephalopathy. J Neurol Neurosurg Psychiatry 69: 74-81.
Ulrich JD & Holtzman DM (2016). TREM2 Function in Alzheimer's Disease and Neurodegeneration. ACS Chem Neurosci.
Uryu K, Chen XH, Martinez D, et al. (2007). Multiple proteins implicated in neurodegenerative diseases accumulate in axons after brain trauma in humans. Exp Neurol 208: 185-192.
Wallin A, Blennow K, Fredman P, et al. (1990). Blood brain barrier function in vascular dementia. Acta Neurol Scand 81: 318-322.
Wallin AK, Blennow K, Zetterberg H, et al. (2010). CSF biomarkers predict a more malignant outcome in Alzheimer disease. Neurology 74: 1531-1537.
Vandermeeren M, Mercken M, Vanmechelen E, et al. (1993). Detection of tau proteins in normal and Alzheimer's disease cerebrospinal fluid with a sensitive sandwich enzyme-linked immunosorbent assay. J Neurochem 61: 1828-1834.
Wang L, Fagan AM, Shah AR, et al. (2012). Cerebrospinal fluid proteins predict longitudinal hippocampal degeneration in early-stage dementia of the Alzheimer type. Alzheimer Dis Assoc Disord 26: 314-321.
Warren JD, Rohrer JD & Rossor MN (2013). Clinical review. Frontotemporal dementia. Bmj 347: f4827.
Watabe-Rudolph M, Song Z, Lausser L, et al. (2012). Chitinase enzyme activity in CSF is a powerful biomarker of Alzheimer disease. Neurology 78: 569-577.
Wellington H, Paterson RW, Portelius E, et al. (2016). Increased CSF neurogranin concentration is specific to Alzheimer disease. Neurology 86: 829-835.
Wennstrom M, Surova Y, Hall S, et al. (2013). Low CSF levels of both alpha-synuclein and the alpha-synuclein cleaving enzyme neurosin in patients with synucleinopathy. PLoS ONE 8: e53250.
Westin K, Buchhave P, Nielsen H, et al. (2012). CCL2 is associated with a faster rate of cognitive decline during early stages of Alzheimer's disease. PLoS ONE 7: e30525.
Weston PS, Paterson RW, Modat M, et al. (2015). Using florbetapir positron emission tomography to explore cerebrospinal fluid cut points and gray zones in small sample sizes. Alzheimers Dement (Amst) 1: 440-446.

Whittington RA, Bretteville A, Dickler MF, et al. (2013). Anesthesia and tau pathology. Prog Neuropsychopharmacol Biol Psychiatry 47: 147-155.
Williams CT, Barnes BM, Richter M, et al. (2012). Hibernation and circadian rhythms of body temperature in free-living Arctic ground squirrels. Physiol Biochem Zool 85: 397-404.
Wiltfang J, Esselmann H, Bibl M, et al. (2007). Amyloid beta peptide ratio 42/40 but not A beta 42 correlates with phospho-Tau in patients with low- and high-CSF A beta 40 load. J Neurochem 101: 1053-1059.
Winblad B, Amouyel P, Andrieu S, et al. (2016). Defeating Alzheimer's disease and other dementias: a priority for European science and society. Lancet Neurol 15: 455-532.
Wischik CM, Novak M, Thogersen HC, et al. (1988). Isolation of a fragment of tau derived from the core of the paired helical filament of Alzheimer disease. Proc Natl Acad Sci U S A 85: 4506-4510.
Visser PJ, Verhey F, Knol DL, et al. (2009). Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study. Lancet Neurol 8: 619-627.
Yin GN, Jeon H, Lee S, et al. (2009). Role of soluble CD14 in cerebrospinal fluid as a regulator of glial functions. J Neurosci Res 87: 2578-2590.
Zetterberg H, Hietala MA, Jonsson M, et al. (2006). Neurochemical aftermath of amateur boxing. Arch Neurol 63: 1277-1280.
Zetterberg H, Pedersen M, Lind K, et al. (2007). Intra-individual stability of CSF biomarkers for Alzheimer's disease over two years. J Alzheimers Dis 12: 255-260.