Clinical Biochemistry 72 (2019) 24–29

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Review

Differential diagnosis between Alzheimer's disease and other dementias: Role of cerebrospinal fluid biomarkers

Lucia Farotti, Federica Nicoletta Sepe, Andrea Toja, Roberta Rinaldi, Lucilla Parnetti*

Centre for Memory Disturbances, Laboratory of Clinical Neurochemistry, Section of Neurology, Department of Medicine, University of Perugia, Perugia, Italy

1. Introduction

Before the biomarkers era, Alzheimer's disease (AD) was diagnosed at dementia stage, based on clinical criteria. In the last decades, the definition of AD has changed from a clinico-pathological entity to a clinico-biological entity, since the underlying pathological processes can be documented in vivo by biomarkers [1]. Cerebrospinal fluid (CSF) represents a unique source of information about the molecular changes occurring in the brain during the disease course. Accordingly, use of CSF biomarkers provides the opportunity to diagnose AD with higher degrees of sensitivity and specificity earlier in the disease continuum, as compared with clinical diagnosis alone. Learning from the lesson of AD, many misfolding and/or aggregating proteins involved in neurodegenerative diseases are under study as novel biomarker candidates, both in dementia and movement disorders. This review provides a contemporary clinical and laboratory framework for CSF biomarker testing both in clinical and research settings. At first, we focus on use of classical AD biomarkers as diagnostic and prognostic tools. Then, novel biomarker candidates are discussed in order to enrich this scenario.

2. Diagnostic tools in degenerative dementias

Recommendations for the appropriate use of CSF biomarkers must be made in the context of the many other diagnostic tools in use [2]. First, the patient's history obtained from an informant provides information on changes in memory, behavior and function over time. Secondly, a neurological examination may reveal signs of other neurodegenerative disorders. In clinical setting, routine blood tests are typically recommended to rule out other causes of or contributors to cognitive impairment (blood counts, blood chemistries, vitamin B12 and thyroid-stimulating hormone levels). Cerebrovascular disease and brain atrophy can be detected using neuroimaging (computed tomography scan or magnetic resonance imaging). Objective neuropsychological tests are useful in documenting presence, type and severity of cognitive decline, but they are not themselves diagnostic. If, after completion of all these evaluations, the etiology of cognitive impairment has not been identified, certain advanced diagnostic procedures can be helpful [2]. In this context, lumbar puncture for CSF biomarkers testing is a reliable and cost-effective tool to obtain information about the pathological processes underpinning the clinical presentation (Box 1 and Box 2). Amyloid PET may support the diagnosis of AD identifying significant quantities of neuritic plaques in the brain [3]. If compared to amyloid PET, CSF analysis has the advantage to incorporate both amyloid and neurodegeneration parameters, and to require less complex and costly instruments. On the other hand, amyloid PET is less invasive and has higher reliability between Centers. Finally, in selected cases fluorodeoxyglucose PET may be helpful in the differential diagnosis between neurodegenerative disorders. This comes particularly significant in case of atypical presentations and in case of uncertain CSF biomarkers results [4].

3. Cerebrospinal fluid biomarkers

3.1. Classical AD biomarkers

The hallmark histological signs of AD include extracellular accumulation of amyloid plaques, intraneuronal neurofibrillary tangles (NFTs) consisting of phosphorylated tau and brain atrophy due to neuronal and synaptic/axonal degeneration [5]. The proximity of CSF to central nervous system makes this biofluid the ideal source for diagnostic markers of the ongoing pathology. Three core CSF biomarkers for AD have been developed, each correlating to one of the key pathological hallmark: low levels of CSF amyloid β 1–42 ($A\beta_{42}$), that correlate with greater plaque load, high levels of phosphorylated tau (p-tau), correlating with NFTs pathology, and high levels of total tau (t-tau), that correlate with neuronal degeneration [6]. According to the research framework of National Institute on Aging and Alzheimer's Association (NIA-AA), AD is defined by its underlying pathologic processes that can be documented in vivo by biomarkers. Biomarkers are grouped into those of β amyloid deposition, pathologic tau, and neurodegeneration [AT(N)] [1]. Since in AD patients amyloid deposition is closely associated with NFTs pathology, the Authors agreed that the term “Alzheimer's disease” should be applied if biomarker evidence of both Aβ and pathologic tau is present (i.e. low $A\beta_{42}$ and elevated p-tau), regardless the positivity of t-tau. This definition is independent from disease stage, covering the continuum from preclinical to dementia

* Corresponding Author at: Department of Medicine, University of Perugia, P.le Severi 1, 06132 Perugia, Italy.
E-mail address: lucilla.parnetti@unipg.it (L. Parnetti).

https://doi.org/10.1016/j.clinbiochem.2019.04.011
Received 30 March 2019; Accepted 13 April 2019
Available online 15 April 2019

Box 1
Lumbar puncture

Lumbar puncture (LP) represents a basic diagnostic procedure for neurological diseases [53]. It consists of the insertion of a spinal needle between L3-L4 or L4-L5 spaces; the needle should reach the CSF, passing through various anatomical layers (skin, subcutaneous tissue, sopraspinous, spinous and flavum ligaments, epidural space and dura). Negative predictive factor for an unsuccessful procedure is high body mass index. Back pain and headache (post lumbar puncture headache and aspecific headache) are the most frequent complications [54]. Use of atraumatic needle is recommended, in the measure that it reduces incidence of post LP headache and back pain [55]. Contraindicating factors have to be excluded before the procedure, like cerebral masses causing brain shift, stenosis or spinal compressions above the site of puncture, local infections, spinal or cranial developmental abnormalities, uncorrected bleeding diathesis. Use of anticoagulant therapy represents an absolute contraindication and requires discontinuation before the procedure, while no major issues regarding antiplatelet therapy have to be raised [55]. Preanalytical and analytical aspects of CSF biomarker testing are of utmost importance both in clinical and research context[4]. Recommendations include the use of polypropylene tubes to collect CSF (since Aβ peptides particularly bind to glass or polystyrene), and that laboratories should be compliant to standard operating procedures, in order to reduce variability among Centers. There is no evidence that fasting condition or time of CSF collection can alter CSF AD biomarker profile [56].

Box 2
Key CSF biomarkers in clinical and research setting

- $A\beta_{42}$: has the highest propensity for aggregation and appears to be the predominant species into plaques, reflecting brain amyloid deposition. Low $A\beta_{42}$ levels have been found in the CSF of AD patients allowing discrimination from healthy subjects [1].
- $A\beta_{42}/A\beta_{40}$ ratio: "normalizes" the CSF $A\beta_{42}$ levels according to the total amyloid load in the brain, expressed by $A\beta_{40}$ levels (the most abundant amyloid peptide in CSF). $A\beta_{42}/A\beta_{40}$ ratio increases the level of precision in detecting AD during both pre-dementia and dementia stages [57].
- T-tau: a surrogate marker of neurodegeneration elevated in AD and other neurodegenerative diseases, although not in all tauopathies. Tau may not be a simple damage biomarker, but is secreted from cells under physiological conditions, a process which is regulated by neuronal activity [1].
- P-tau: p-tau reflects phosphorylation state of tau and correlates with intraneuronal neurofibrillary tangles; high levels of p-tau are more specific for AD than t-tau [1].
- Neurofilament Light: is a marker of large fiber myelinated axonal degeneration; it is elevated in neurodegeneration independently of amyloid deposition and has been shown to be a diagnostic and prognostic marker in a large number of different neurodegenerative conditions [28].
- α-synuclein: a presynaptic molecule that plays a role in modulating vescicular synaptic release and in regulation of synaptic plasticity. CSF total α-synuclein levels seem to be decreased in synucleinopathies compared to other neurodegenerative disorders and to healthy subjects. More recently, specific α-synuclein species such as oligomeric and phosphorylated forms have been considered as potential biomarkers, as oligomerization precedes aggregation into mature fibrils and phosphorylated form of α-syn is highly represented in Lewy bodies [40,41,58].

stages, and independent from clinical presentations, as CSF profiles of typical and atypical AD are remarkably similar [1,7]. In clinical practice, the use of CSF AD biomarkers is of utmost importance i) to differentiate between dementias and, in particular, to confirm/exclude AD diagnosis; ii) to detect the presence of mixed pathologies.

3.1.1. Role of classical AD biomarkers in differential diagnosis

Classical AD biomarkers have been extensively evaluated in differential diagnosis between dementias. In 2015, a large cohort of 5676 patients with a clinical diagnosis of dementia was included in a study aimed to evaluate the associations of CSF biomarkers with clinical diagnosis [8]. Patients included were diagnosed as early onset AD, late onset AD, frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD), vascular dementia, mixed AD & vascular dementia, dementia not otherwise specified and other dementias (i.e. corticobasal syndrome, alcohol-related dementias). For all these patients, a complete set of measurements for CSF $A\beta_{42}$, t-tau and p-tau were available. Using cluster analysis, disregarding clinical diagnosis, the optimal separation of this data set was into two clusters, with the majority of patients with early onset AD (75%) and late onset AD (73%) assigned to one cluster and the patients with vascular dementia (91%), FTD (94%), PDD (94%) and DLB (87%) to the other cluster. As expected, the lowest levels of $A\beta_{42}$ and $A\beta_{42}$/p-tau ratios and the highest levels of t-tau and p-tau were found in AD. With respect to non-AD dementias, FTD patients revealed the highest CSF levels of $A\beta_{42}$ and the lowest levels of t-tau and p-tau. Therefore, subjects with FTD had a CSF biomarker profile most distinct from AD [8]. These findings have been confirmed by other studies. According to a recent systematic review, the p-tau/$A\beta_{42}$ ratio shows the best diagnostic performance in the differential diagnosis between AD and FTD [9]. These results are in concordance with the lack of cerebral β-amyloidosis and NFTs in FTD, and confirm the usefulness of CSF biomarkers in differential diagnosis, especially in case of atypical presentations (i.e. frontal variant AD vs. behavioral variant FTD).

With respect to the Lewy Body disorders (LBDs), studies have shown a biomarker evidence of concomitant AD pathology, especially in the dementia phase. In the large cohort of Skillback and coll. (2015), DLB showed a significant decrease of $A\beta_{42}$ levels in 71% of cases, while for PDD, 53% had pathological reduction of $A\beta_{42}$. No significant differences in biomarker levels between DLB and PDD group were observed. More recently, a multicenter cohort study investigated the prevalence of AD CSF biomarkers across the spectrum of LBDs (375 DLB, 55 PDD and 164 PD). A large proportions of DLB patients had abnormal values of $A\beta_{42}$ (49%), t-tau (28%), and p-tau (32%), while proportions were far lower in PD ($A\beta_{42}$: 12%; t-tau: 4%, p-tau: 7%). The prevalence of abnormal AD biomarkers in PDD was in between ($A\beta_{42}$: 42%; t-tau: 17%; p-tau: 6%). A CSF profile compatible with AD (abnormal $A\beta_{42}$ combined with abnormal t-tau and/or p-tau) was observed in almost 25% of DLB patients, compared with only 9% of the PDD patients ($p < .05$) and 3% of the PD patients ($p < .001$) [8].

Relevance of AD biomarkers in the differential diagnosis between DLB and AD has been extensively reviewed elsewhere [10]. Tau species (t-tau and p-tau) seem to be useful biomarkers for discriminating AD from DLB, with higher levels in AD patients and lower – or even unchanged - values in DLB. According to studies, sensitivity may vary from 75 to 94% for p-tau and from 72 to 79% for t-tau. Specificity ranges from 61 to 94% for p-tau and from 64 to 76% for t-tau [10]. As already reported, pathologic levels of $A\beta_{42}$ are frequently observed in DLB patients. Comparing AD and DLB, some studies found more reduced $A\beta_{42}$ levels in DLB [11,12], while others in AD [13]. Finally,

some studies indicated not statistically significant differences in DLB patients compared to AD [14,15]. In differential diagnosis between AD and DLB, $A\beta_{42}$ has good specificity (94%) but low sensitivity (48%) [13]. The discriminative power of $A\beta_{42}$ could be improved using the $A\beta_{42}/A\beta_{40}$ ratio, even if only a few studies have investigated this issue [16]. Finally, it should be underlined that in DLB patients, $A\beta_{42}$ levels seem to be poorly impacted at prodromal stage, with a later decrease of $A\beta_{42}$ in the dementia phase [17]. These findings could be explained by the fact that amyloid deposits appear later in DLB, after aggregation of α-synuclein (α-syn). In the context of early diagnosis, positivity of CSF $A\beta_{42}$ in mild cognitive impairment (MCI) patients may support the diagnosis of prodromal AD, ruling out the diagnosis of DLB.

Some neurodegenerative disorders show rapid evolution of cognitive decline, usually with coexistence of motor signs and other focal symptoms. In these cases, Creutzfeldt-Jakob disease (CJD) diagnosis needs to be excluded. Classical AD biomarkers can be useful in clinical practice to distinguish atypical clinical AD presentations from CJD. The levels of t-tau and the t-tau/p-tau ratio in atypical AD seem to be significantly higher than in typical AD but significantly lower than in CJD. Levels of p-tau are significantly higher in atypical AD than in patients with typical AD and in patients with CJD. Lower values of $A\beta_{42}$ and $A\beta_{42}$/p-tau in atypical AD than in typical AD and CJD have been described [18]. Regarding t-tau and p-tau levels, similar results were previously reported elsewhere [19].

Overall, all these studies demonstrate the feasibility of applying CSF biomarker studies to very large populations, and support the utility of CSF biomarkers in distinguish between dementias in routine clinical settings.

3.1.2. Role of classical AD biomarkers in prognosis

Classical AD biomarkers have been investigated as prognostic factors in LBDs. Reduced CSF $A\beta_{42}$ has been demonstrated as an independent predictor of long-term cognitive decline in patients with PD [20,21]. Similarly, reduced levels of CSF $A\beta_{42}$ resulted associated with more rapid cognitive decline in DLB patients [22]. Interestingly, in the Parkinson's Progression Markers Initiative cohort of newly diagnosed PD, reduced levels of $A\beta_{42}$ were associated with higher risk of early onset psychosis. No associations with total tau, p-tau or α-syn were reported [23]. With respect to motor progression, low baseline CSF $A\beta_{42}$, and to a lesser extend $A\beta_{40}$, seem to predict progression of dopa-resistant gait impairments in PD [24]. CSF p-tau has been found to correlate with worsening of motor symptoms as measured by means of Unified Parkinson's Disease Rating Scale, Part III (UPDRS-III) score [25,26]. Similarly, longitudinal changes in CSF t-tau positively correlated with total UPDRS and UPDRS-III scores increase over time [27]. These observations are consistent with previous findings showing that AD pathology may contribute to cognitive impairment and motor progression in LBDs. Recognition of the presence of a CSF AD biomarker profile may advance patient management and individualization of treatment strategies. In addition, disease-modifying treatment strategies targeting amyloid and tau aggregates, which are currently under development for AD, may have clinical value in LBDs as well.

3.2. Neurofilaments

Neurofilaments (Nfs) are exclusively expressed in neurons and represent candidate biomarkers of neuroaxonal injury. Indeed, they reach abnormal levels as a result of extent axonal damage in neurodegenerative, inflammatory, vascular and traumatic diseases both in the CSF and in blood [28]. Nfs are classified as intermediate filaments according to their diameter (~10 nm). They are hetero-polymers composed of NfL (human neurofilaments light chain, 68 kDa), NfM (human neurofilaments medium chain, 160 kDa), NfH (human neurofilaments heavy chain, 260 kDa) and alpha-internexin and peripherin subunits [29]. The precise functions of Nfs remain unknown, but they are thought to have a direct role in radial growth and stability of axons, which is critical for effective nerve conduction, organelle distribution along axons and synaptic plasticity [28]. In the last few years, a significant improvement in the analytical sensitivity of the assays suitable for measuring Nfs levels in CSF and blood has been reached [28]. This allowed evaluation of the diagnostic and prognostic role of Nfs in many neurological disorders, such as amyotrophic lateral sclerosis, multiple sclerosis and neuromyelitic optic spectrum disorders, stroke, traumatic spinal cord and brain injury, dementias and movement disorders, epilepsy, hypoxic brain injury, encephalitis, intracranial pressure, peripheral neuropathies including Guillain-Barrè syndrome and also psychiatric disorders [28].

With respect to neurodegenerative dementias, CSF levels of NfL resulted increased during the MCI and dementia stages of AD, even if the diagnostic specificity of NfL was lower than that of the hallmark AD biomarkers [30,31]. In a study led by Skillbac and colleagues, CSF NfL levels were analyzed in 3356 individuals with dementia. Both t-tau and p-tau had positive correlations with NfL, whereas $A\beta_{42}$ had an inverse correlation. Subjects with a positive AD biomarker profile often showed high NfL levels, suggesting an association between AD and subcortical axonal degeneration [32].

In 2018, an Italian group tested NfL alone and in combination with classical AD biomarkers in atypical/rapidly progressive neurodegenerative dementias. CSF NfL, t-tau, p-tau, and $A\beta_{42}$ were analyzed in 323 subjects with a neuropathological or clinical diagnosis of prion disease, AD, DLB, or fronto-temporal lobar degeneration (FTLD). In each patient group CSF NfL showed higher levels than in control subjects, reaching the highest values in those with CJD. High NfL levels were detected in most atypical CJD cases. Similarly, rapidly progressive/atypical cases showed higher NfL levels than typical patients in FTLD, but not in AD or DLB [33].

Recently, Meeter and colleagues examined the clinical value of NfL and the p-tau/t-tau ratio across the entire FTD spectrum (behavioral variant of FTD, FTD with motor neuron disease, semantic, non-fluent and logopenic variant of primary progressive aphasia, corticobasal syndrome and progressive supranuclear palsy) compared to cognitively healthy controls. NfL levels resulted higher in all diagnoses (except logopenic variant) than in controls and highest in FTD with motor neuron disease. Conversely, p-tau/t-tau was lower in all clinical groups (except logopenic variant) and lowest in FTD with motor neuron disease. Both high NfL and low p-tau/t-tau were associated with poor survival and can be considered promising prognostic biomarkers [34].

In the context of movement disorders, CSF NfL concentrations seem to be significantly increased in multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) with respect to PD, helping to separate PD from atypical parkinsonian syndromes [35,36]. These results have been more recently confirmed by a meta-analysis [37]. Similarly, high CSF NfL levels have been described also in corticobasal degeneration (CBD) [38]. Finally, a prognostic role of NfL has been described in PSP, being CSF NfL able to predict disease progression [39].

3.3. Alpha synuclein species

The discovery of α-syn as a major component of Lewy bodies (LBs) and the detection of α-syn in CSF have encouraged research into α-syn as a potential biomarker for LBDs, in particular for PD and DLB. The discriminating value of CSF total α-syn (t-α-syn) has been addressed in multiple studies. More recently, specific α-syn species, such as oligomeric α-syn (o-α-syn) and phosphorylated α-syn at residue Ser129 (p-α-syn), have been considered as potential diagnostic biomarkers. Indeed, the oligomerization of α-syn precedes its aggregation into mature amyloid fibrils in LBs, and studies provide evidences that soluble oligomers of α-syn are neurotoxic in vitro and in vivo [40]. Since approximately 90% of accumulated α-syn in LBs consists of p-α-syn, it has been considered an interesting biomarker candidate of synucleinopathies [41].

Table 1
Features that increase the likelihood of preclinical AD in individuals with SCD: SCD *plus* [52].

- Persistent subjective decline in memory rather than other cognitive domains
- Onset within the last 5 years
- Age at onset ≥ 60 years
- Concerns (worries) associated with SCD
- Feeling of worse performance than others of the same age group

If available or possible to obtain:

- Confirmation of cognitive decline by an informant
- Presence of apolipoprotein ε4 genotype
- Biomarker evidence for AD (preclinical AD is defined)

3.3.1. Role of α-synuclein species in diagnosis

According to several studies [42–44] and recent meta-analysis [45], CSF t-α-syn resulted significantly lower in PD patients compared to healthy controls and other neurological disorders. Furthermore, most of studies have shown that the total levels of α-syn in the CSF are significantly decreased in patients with PD compared with AD patients [42,44] and that t-α-syn is able to distinguish PDD from AD patients [44,46], reaching an AUC of 0.80 [46]. Interestingly, increased levels of CSF total but not oligomeric or phosphorylated forms of α-syn in patients diagnosed with AD have been reported, with respect to neurological controls [47].

CSF o-α-syn has been consistently found to be higher in PD patients compared to other neurological disorders [21,48] and healthy controls [43]. In the comparison between PDD and AD, CSF levels of o-α-syn resulted significantly higher in patients with PDD ($p < .01$), and also the o-α-syn/t-α-syn ratio was elevated in PDD patients compared with AD patients [46].

Only a few studies have focused on CSF p-α-syn as a diagnostic marker, finding increased levels in PD compared to controls and to PSP [45]. Similar to o-α-syn, its diagnostic accuracy increases when considered together with other α-syn species and neurodegenerative biomarkers (o-α-syn/t-α-syn ratio together with p-α-syn and p-tau) [43].

CSF α-syn species levels in DLB resulted very similar to the pattern observed in PD and PDD. Indeed, t-α-syn was found to be reduced in DLB with respect to controls and AD [42,44]. Regarding o-α-syn, its levels resulted higher in DLB compared with controls [42] and increased levels of o-α-syn and elevated o-α-syn/t-α-syn ratio have been described in DLB patients compared with AD [42,46]. In differential diagnosis, the most promising results have been observed combining α-syn species with classical AD biomarkers, with the combination of tau and o-α-syn reaching an AUC of 0.83 in the differentiation of DLB from AD. These results are particularly remarkable due to the significant overlap of symptoms between AD and DLB [42].

3.3.2. Role of α-synuclein species in prognosis

Regarding the possible use of α-syn species as prognostic markers, different studies gave contrasting results. One study showed a positive association between t-α-syn and Hohen&Yahr (H&Y) stage, UPDRS-III and prolonged Timed Up and Go test over 2 years [25], suggesting that increased α-syn might be a marker of more intense synaptic degeneration in PD. Similar results have been found with CSF o-α-syn/t-α-syn ratio, in particular in the postural-instability and gait-difficulty dominant PD [49]. However, according to other studies, no significant association between baseline CSF t-α-syn and subsequent motor progression in PD was found [26,50].

Differently from CSF $A\beta_{42}$, biomarkers of synucleinopathy have shown conflicting results as predictor of cognitive impairment in LBDs. Both high CSF t-α-syn [25] and low CSF t-α-syn [51] has been identified as predictors of cognitive decline in PD, while in other reports no prognostic effect of CSF t-α-syn and o-α-syn has been found [21,26,50].

In conclusion, further studies on CSF α-syn species are required to confirm their potential diagnostic and prognostic value in neurodegenerative disorders.

4. Conclusions

In clinical routine, recommendations for the use of CSF biomarkers must be made in the context of confirmation or exclusion of AD diagnosis. Despite many limitations of currently available medical interventions for AD, an early and accurate diagnosis forms the basis of excellent medical care. CSF confirmation of AD may ensure clinical care early in the disease process, adjustments for daily life activities (work responsibilities, driving and financial planning), and opportunities to participate in clinical trials.

In 2017 the Alzheimer's Association convened a multidisciplinary workgroup to develop appropriate use criteria to guide the optimal use of CSF testing for AD pathology detection [2]. The document focuses on CSF $A\beta_{42}$ (sometimes normalized to the related peptide $A\beta_{40}$), t-tau and p-tau. The clinical indications include: i) patients with subjective cognitive decline (SCD - cognitively unimpaired based on objective testing) who are considered to be at increased risk for AD (SCD *plus* – see Table 1); ii) MCI that is persistent, progressing and unexplained; iii) patients with symptoms that suggest atypical AD or mixed pathology (possible AD); iv) MCI or dementia with an onset at an early age (< 65 years); v) some cases meeting core clinical criteria for probable AD with typical age of onset (i.e. uncertain clinical judgment, major life decisions based on diagnosis); vi) patients whose dominant symptom is a change in behavior and where AD diagnosis is being considered. In all these conditions, CSF biomarker testing should be conducted by dementia experts. This would ensure that patient and family are correctly informed about the benefits and risks of testing, and that the procedure is performed with reliable assays following established guidelines [2]. Classical AD biomarkers ($A\beta_{42,}$ t-tau and p-tau) are particularly useful in the differential diagnosis between AD and FTD and between atypical AD and CJD. Furthermore, $A\beta_{42}$ revealed a significant role as predictor of cognitive impairment both in PD and DLB, encouraging its use in clinical practice. NfL, reflecting neuroaxonal damage, represent a promising diagnostic and prognostic biomarker for FTD and other neurodegenerative diseases. Regarding CSF α-syn species, lower levels of t-α-syn and higher concentration of oligomeric and phosphorylated-α-syn have been observed in PD and DLB with respect to controls. At present, neither NfL nor α-syn species could be considered specific biomarkers for neurological diseases, and their use in clinical routine is not feasible. Methodological factors, patient selection, variation in storage and processing steps, and blood contamination should be taken into account to improve reliability of findings. Finally, combination of several biomarkers could enrich our diagnostic and prognostic tools in neurodegenerative disorders.

References

[1] C.R. Jack, D.A. Bennett, K. Blennow, M.C. Carrillo, B. Dunn, S.B. Haeberlein, D.M. Holtzman, W. Jagust, F. Jessen, J. Karlawish, E. Liu, J.L. Molinuevo, T. Montine, C. Phelps, K.P. Rankin, C.C. Rowe, P. Scheltens, E. Siemers, H.M. Snyder, R. Sperling, C. Elliott, E. Masliah, L. Ryan, N. Silverberg, NIA-AA research framework: toward a biological definition of Alzheimer's disease, Alzheimer's Dement. (2018), https://doi.org/10.1016/j.jalz.2018.02.018.

[2] L.M. Shaw, J. Arias, K. Blennow, D. Galasko, J.L. Molinuevo, S. Salloway, S. Schindler, M.C. Carrillo, J.A. Hendrix, A. Ross, J. Illes, C. Ramus, S. Fifer, Appropriate use criteria for lumbar puncture and cerebrospinal fluid testing in the diagnosis of Alzheimer's disease, Alzheimers Dement. 14 (2018) 1505–1521, https://doi.org/10.1016/j.jalz.2018.07.220.

[3] A. Mallik, A. Drzezga, S. Minoshima, Clinical amyloid imaging, Semin. Nucl. Med. 47 (2017) 31–43, https://doi.org/10.1053/j.semnuclmed.2016.09.005.

[4] N.L. Foster, J.L. Heidebrink, C.M. Clark, W.J. Jagust, S.E. Arnold, N.R. Barbas, C.S. DeCarli, R. Scott Turner, R.A. Koeppe, R. Higdon, S. Minoshima, FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease, Brain. 130 (2007) 2616–2635, https://doi.org/10.1093/brain/awm177.

[5] K. Blennow, M.J. De Leon, H. Zetterberg, Seminar Alzheimer's disease, Lancet Neurol. 368 (2006) 387–403.

[6] K. Blennow, H. Hampel, M. Weiner, H. Zetterberg, Cerebrospinal fluid and plasma biomarkers in Alzheimer disease, Nat. Rev. Neurol. 6 (2010) 131–144, https://doi.org/10.1038/nrneurol.2010.4.

[7] R.W. Paterson, J. Toombs, C.F. Slattery, J.M. Nicholas, U. Andreasson, N.K. Magdalinou, K. Blennow, J.D. Warren, C.J. Mummery, M.N. Rossor, M.P. Lunn,

S.J. Crutch, N.C. Fox, H. Zetterberg, J.M. Schott, Dissecting IWG-2 typical and atypical Alzheimer's disease: insights from cerebrospinal fluid analysis, J. Neurol. 262 (2015) 2722–2730, https://doi.org/10.1007/s00415-015-7904-3.
[8] T. Skillbäck, B.Y. Farahmand, C. Rosén, N. Mattsson, K. Nägga, L. Kilander, D. Religa, A. Wimo, B. Winblad, J.M. Schott, K. Blennow, M. Eriksdotter, H. Zetterberg, Cerebrospinal fluid tau and amyloid-β < inf > 1-42 < /inf > in patients with dementia, Brain. 138 (2015) 2716–2731, https://doi.org/10.1093/brain/awv181.
[9] A. Rivero-Santana, D. Ferreira, L. Perestelo-Pérez, E. Westman, L.O. Wahlund, A. Sarría, P. Serrano-Aguilar, Cerebrospinal fluid biomarkers for the differential diagnosis between Alzheimer's disease and frontotemporal lobar degeneration: systematic review, HSROC analysis, and confounding factors, J. Alzheimers Dis. 55 (2017) 625–644, https://doi.org/10.3233/JAD-160366.
[10] O. Bousiges, F. Blanc, Diagnostic value of cerebro-spinal fluid biomarkers in dementia with lewy bodies, Clin. Chim. Acta 490 (2019) 222–228, https://doi.org/10.1016/j.cca.2018.11.027.
[11] L. Parnetti, P. Tiraboschi, A. Lanari, M. Peducci, C. Padiglioni, C. D'Amore, L. Pierguidi, N. Tambasco, A. Rossi, P. Calabresi, Cerebrospinal fluid biomarkers in Parkinson's disease with dementia and dementia with Lewy bodies, Biol. Psychiatry 64 (2008) 850–855, https://doi.org/10.1016/j.biopsych.2008.02.016.
[12] L. Kaerst, A. Kuhlmann, D. Wedekind, K. Stoeck, P. Lange, I. Zerr, Using cerebrospinal fluid marker profiles in clinical diagnosis of dementia with lewy bodies, Parkinson's disease, and Alzheimer's disease, J. Alzheimers Dis. 38 (2014) 63–73, https://doi.org/10.3233/JAD-130995.
[13] M. Bibl, B. Mollenhauer, H. Esselmann, P. Lewczuk, C. Trenkwalder, P. Brechlin, E. Rüther, J. Kornhuber, M. Otto, J. Wiltfang, CSF diagnosis of Alzheimer's disease and dementia with Lewy bodies, J. Neural Transm. 113 (2006) 1771–1778, https://doi.org/10.1007/s00702-006-0537-z.
[14] H. Vanderstichele, K. De Vreese, K. Blennow, N. Andreasen, C. Sindic, A. Ivanoiu, H. Hampel, K. Bürger, L. Parnetti, A. Lanari, A. Padovani, M. DiLuca, M. Bläser, A. Ohrfelt Olsson, H. Pottel, F. Hulstaert, E. Vanmechelen, Analytical performance and clinical utility of the INNOTEST® PHOSPHO-TAU(181P) assay for discrimination between Alzheimer's disease and dementia with Lewy bodies, Clin. Chem. Lab. Med. (2006), https://doi.org/10.1515/CCLM.2006.258.
[15] K. Kasuga, T. Tokutake, A. Ishikawa, T. Uchiyama, T. Tokuda, O. Onodera, M. Nishizawa, T. Ikeuchi, Differential levels of α-synuclein, β-amyloid42 and tau in CSF between patients with dementia with Lewy bodies and Alzheimer's disease, J. Neurol. Neurosurg. Psychiatry 81 (2010) 608–610, https://doi.org/10.1136/jnnp.2009.197483.
[16] P.E. Spies, D. Slats, J.M.C. Sjogren, B.P.H. Kremer, F.R.J. Verhey, M.G.M. Olde Rikkert, M.M. Verbeek, The cerebrospinal fluid amyloid β42/40 ratio in the differentiation of Alzheimers Disease from Non-Alzheimers Dementia, Curr. Alzheimer Res. 7 (2010) 470–476, https://doi.org/10.2174/156720510791383796.
[17] O. Bousiges, S. Bombois, S. Schraen, D. Wallon, M.M. Quillard, A. Gabelle, S. Lehmann, C. Paquet, E. Amar-Bouaziz, E. Magnin, C. Miguet-Alfonsi, X. Delbeuck, T. Lavaux, P. Anthony, N. Philippi, F. Blanc, Cerebrospinal fluid Alzheimer biomarkers can be useful for discriminating dementia with Lewy bodies from Alzheimer's disease at the prodromal stage, J. Neurol. Neurosurg. Psychiatry (2018), https://doi.org/10.1136/jnnp-2017-316385.
[18] A. Dorey, Y. Tholance, A. Vighetto, A. Perret-Liaudet, I. Lachman, P. Krolak-Salmon, U. Wagner, H. Struyfs, P.P. De Deyn, B. El-Moualij, W. Zorzi, D. Meyronet, N. Streichenberger, S. Engelborghs, G.G. Kovacs, I. Quadrio, Association of cerebrospinal fluid prion protein levels and the distinction between Alzheimer disease and Creutzfeldt-Jakob disease, JAMA Neurol. 72 (2015) 267–275, https://doi.org/10.1001/jamaneurol.2014.4068.
[19] T. Skillbäck, C. Rosén, F. Asztely, N. Mattsson, K. Blennow, H. Zetterberg, Diagnostic performance of cerebrospinal fluid total tau and phosphorylated tau in Creutzfeldt-Jakob disease: results from the Swedish mortality registry, JAMA Neurol. 71 (2014) 476–483, https://doi.org/10.1001/jamaneurol.2013.6455.
[20] A. Siderowf, S.X. Xie, H. Hurtig, D. Weintraub, J. Duda, A. Chen-Plotkin, L.M. Shaw, V. Van Deerlin, J.Q. Trojanowski, C. Clark, CSF amyloid β 1-42 predicts cognitive decline in Parkinson disease, Neurology. 75 (2010) 1055–1061, https://doi.org/10.1212/WNL.0b013e3181f39a78.
[21] L. Parnetti, L. Farotti, P. Eusebi, D. Chiasserini, C. De Carlo, D. Giannandrea, N. Salvadori, V. Lisetti, N. Tambasco, A. Rossi, N.K. Majbour, O. El-Agnaf, P. Calabresi, Differential role of csf alpha-synuclein species, tau, and Aβ42 in Parkinson's Disease, Front. Aging Neurosci. (2014). doi:https://doi.org/10.3389/fnagi.2014.00053.
[22] C. Abdelnour, I. van Steenoven, E. Londos, F. Blanc, B. Auestad, M.G. Kramberger, H. Zetterberg, B. Mollenhauer, M. Boada, D. Aarsland, Alzheimer's disease cerebrospinal fluid biomarkers predict cognitive decline in lewy body dementia, Mov. Disord. 31 (2016) 1203–1208, https://doi.org/10.1002/mds.26668.
[23] D.H. Ffytche, J.B. Pereira, C. Ballard, K.R. Chaudhuri, D. Weintraub, D. Aarsland, Risk factors for early psychosis in PD: insights from the Parkinson's progression markers initiative, J. Neurol. Neurosurg. Psychiatry 88 (2017) 325–331, https://doi.org/10.1136/jnnp-2016-314832.
[24] L. Rochester, B. Galna, S. Lord, A.J. Yarnall, R. Morris, G. Duncan, T.K. Khoo, B. Mollenhauer, D.J. Burn, Decrease in Aβ42 predicts dopa-resistant gait progression in early parkinson disease, Neurology (2017), https://doi.org/10.1212/WNL.0000000000003840.
[25] S. Hall, Y. Surova, A. Ohrfelt, H. Zetterberg, D. Lindqvist, O. Hansson, CSF biomarkers and clinical progression of Parkinson disease, Neurology. 84 (2015) 57–63, https://doi.org/10.1212/WNL.0000000000001098.
[26] S. Hall, Y. Surova, A. Öhrfelt, K. Blennow, H. Zetterberg, O. Hansson, Longitudinal measurements of cerebrospinal fluid biomarkers in Parkinson's disease, Mov. Disord. 31 (2016) 898–905, https://doi.org/10.1002/mds.26578.
[27] J. Zhang, H.A. Mattison, C. Liu, C. Ginghina, P. Auinger, M.P. McDermott, T. Stewart, U.J. Kang, K.C. Cain, M. Shi, Longitudinal assessment of tau and amyloid beta in cerebrospinal fluid of Parkinson disease, Acta Neuropathol. 126 (2013) 671–682, https://doi.org/10.1007/s00401-013-1121-x.
[28] M. Khalil, C.E. Teunissen, M. Otto, F. Piehl, M.P. Sormani, T. Gattringer, C. Barro, L. Kappos, M. Comabella, F. Fazekas, A. Petzold, K. Blennow, H. Zetterberg, J. Kuhle, Neurofilaments as biomarkers in neurological disorders, Nat. Rev., Neurol, 2018, https://doi.org/10.1038/s41582-018-0058-z.
[29] A. Yuan, M.V. Rao, Veeranna, R.A. Nixon, Neurofilaments at a glance, J. Cell Sci. (2012), https://doi.org/10.1242/jcs.104729.
[30] B. Olsson, R. Lautner, U. Andreasson, A. Öhrfelt, E. Portelius, M. Bjerke, M. Hölttä, C. Rosén, C. Olsson, G. Strobel, E. Wu, K. Dakin, M. Petzold, K. Blennow, H. Zetterberg, CSF and blood biomarkers for the diagnosis of alzheimer's disease: a systematic review and meta-analysis, Lancet Neurol. (2016), https://doi.org/10.1016/S1474-4422(16)00070-3.
[31] N. Mattsson, P.S. Insel, S. Palmqvist, E. Portelius, H. Zetterberg, M. Weiner, K. Blennow, O. Hansson, Cerebrospinal fluid tau, neurogranin, and neurofilament light in Alzheimer's disease, EMBO Mol. Med. 8 (2016) 1184–1196.
[32] T. Skillbäck, H. Zetterberg, K. Blennow, N. Mattsson, Cerebrospinal fluid biomarkers for Alzheimer disease and subcortical axonal damage in 5,542 clinical samples, Alzheimer's Res. Ther. 5 (2013), https://doi.org/10.1186/alzrt212.
[33] S. Abu-Rumeileh, S. Capellari, M. Stanzani-Maserati, B. Polischi, P. Martinelli, P. Caroppo, A. Ladogana, P. Parchi, The CSF neurofilament light signature in rapidly progressive neurodegenerative dementias, Alzheimers Res. Ther. 10 (2018) 1–11, https://doi.org/10.1186/s13195-017-0331-1.
[34] L.H.H. Meeter, E.G. Vijverberg, M. Del Campo, A.J.M. Rozemuller, L. Donker Kaat, F.J. de Jong, W.M. van der Flier, C.E. Teunissen, J.C. van Swieten, Y.A.L. Pijnenburg, Clinical value of neurofilament and phospho-tau/tau ratio in the frontotemporal dementia spectrum, Neurology. 90 (2018) e1231–e1239, https://doi.org/10.1212/WNL.0000000000005261.
[35] W.F. Abdo, B.R. Bloem, W.J. Van Geel, R.A.J. Esselink, M.M. Verbeek, CSF neurofilament light chain and tau differentiate multiple system atrophy from Parkinson's disease, Neurobiol. Aging 28 (2007) 742–747, https://doi.org/10.1016/j.neurobiolaging.2006.03.010.
[36] B. Holmberg, L. Rosengren, J.-E. Karlsson, B. Johnels, Increased cerebrospinal fluid levels of neurofilament protein in progressive supranuclear palsy and multiple-system atrophy compared with Parkinson's disease, Mov. Disord. 13 (1998) 70–77, https://doi.org/10.1002/mds.870130116.
[37] W. Sako, N. Murakami, Y. Izumi, R. Kaji, Neurofilament light chain level in cerebrospinal fluid can differentiate Parkinson's disease from atypical parkinsonism: evidence from a meta-analysis, J. Neurol. Sci. 352 (2015) 84–87, https://doi.org/10.1016/j.jns.2015.03.041.
[38] R. Constantinescu, L. Rosengren, B. Johnels, H. Zetterberg, B. Holmberg, Consecutive analyses of cerebrospinal fluid axonal and glial markers in Parkinson's disease and atypical parkinsonian disorders, Park. Relat. Disord. 16 (2010) 142–145, https://doi.org/10.1016/j.parkreldis.2009.07.007.
[39] J.C. Rojas, A. Karydas, J. Bang, R.M. Tsai, K. Blennow, V. Liman, J.H. Kramer, H. Rosen, B.L. Miller, H. Zetterberg, A.L. Boxer, Plasma neurofilament light chain predicts progression in progressive supranuclear palsy, Ann. Clin. Transl. Neurol. 3 (2016) 216–225, https://doi.org/10.1002/acn3.290.
[40] K. Vekrellis, M. Xilouri, E. Emmanouilidou, H.J. Rideout, L. Stefanis, Pathological roles of α-synuclein in neurological disorders, Lancet Neurol. 10 (2011) 1015–1025, https://doi.org/10.1016/S1474-4422(11)70213-7.
[41] J.P. Anderson, D.E. Walker, J.M. Goldstein, R. de Laat, K. Banducci, R.J. Caccavello, R. Barbour, J. Huang, K. Kling, M. Lee, L. Diep, P.S. Keim, X. Shen, T. Chataway, M.G. Schlossmacher, P. Seubert, D. Schenk, S. Sinha, W.P. Gai, T.J. Chilcote, Phosphorylation of Ser-129 is the dominant pathological modification of alpha-synuclein in familial and sporadic Lewy body disease, J. Biol. Chem. 281 (2006) 29739–29752, https://doi.org/10.1074/jbc.M600933200.
[42] I. van Steenoven, N.K. Majbour, N.N. Vaikath, H.W. Berendse, W.M. van der Flier, W.D.J. van de Berg, C.E. Teunissen, A.W. Lemstra, O.M.A. El-Agnaf, α-Synuclein species as potential cerebrospinal fluid biomarkers for dementia with lewy bodies, Mov. Disord. 33 (2018) 1724–1733, https://doi.org/10.1002/mds.111.
[43] N.K. Majbour, N.N. Vaikath, K.D. Van Dijk, M.T. Ardah, S. Varghese, L.B. Vesterager, L.P. Montezinho, S. Poole, B. Safieh-Garabedian, T. Tokuda, C.E. Teunissen, H.W. Berendse, W.D.J. Van De Berg, O.M.A. El-Agnaf, Oligomeric and phosphorylated alpha-synuclein as potential CSF biomarkers for Parkinson's disease, Mol. Neurodegener. 11 (2016), https://doi.org/10.1186/s13024-016-0072-9.
[44] S. Hall, A. Öhrfelt, R. Constantinescu, U. Andreasson, Y. Surova, F. Bostrom, C. Nilsson, H. Widner, H. Decraemer, K. Nägga, L. Minthon, E. Londos, E. Vanmechelen, B. Holmberg, H. Zetterberg, K. Blennow, O. Hansson, Accuracy of a panel of 5 cerebrospinal fluid biomarkers in the differential diagnosis of patients with dementia and/or parkinsonian disorders, Arch. Neurol. 69 (2012) 1445–1452, https://doi.org/10.1001/archneurol.2012.1654.
[45] P. Eusebi, D. Giannandrea, L. Biscetti, I. Abraha, D. Chiasserini, M. Orso, P. Calabresi, L. Parnetti, Diagnostic utility of cerebrospinal fluid α-synuclein in Parkinson's disease: a systematic review and meta-analysis, Mov. Disord. 32 (2017) 1389–1400, https://doi.org/10.1002/mds.27110.
[46] O. Hansson, S. Hall, A. Öhrfelt, H. Zetterberg, K. Blennow, L. Minthon, K. Nägga, E. Londos, S. Varghese, N.K. Majbour, A. Al-Hayani, O.M. El-Agnaf, Levels of cerebrospinal fluid α-synuclein oligomers are increased in Parkinson's disease with dementia and dementia with Lewy bodies compared to Alzheimer's disease, Alzheimer's Res. Ther. 6 (2014), https://doi.org/10.1186/alzrt255.
[47] N.K. Majbour, D. Chiasserini, N.N. Vaikath, P. Eusebi, T. Tokuda, W. Van De Berg,

L. Parnetti, P. Calabresi, O.M.A. El-Agnaf, Increased levels of CSF total but not oligomeric or phosphorylated forms of alpha-synuclein in patients diagnosed with probable Alzheimer's disease, Sci. Rep. 7 (2017), https://doi.org/10.1038/srep40263.

[48] T. Tokuda, M.M. Qureshi, M.T. Ardah, S. Varghese, S.A.S. Shehab, T. Kasai, N. Ishigami, A. Tamaoka, M. Nakagawa, O.M.A. El-Agnaf, Detection of elevated levels of -synuclein oligomers in CSF from patients with Parkinson disease, Neurology. 75 (2010) 1766–1770, https://doi.org/10.1212/WNL.0b013e3181fd613b.

[49] N.K. Majbour, N.N. Vaikath, P. Eusebi, D. Chiasserini, M. Ardah, S. Varghese, M.E. Haque, T. Tokuda, P. Auinger, P. Calabresi, L. Parnetti, O.M.A. El-Agnaf, Longitudinal changes in CSF alpha-synuclein species reflect Parkinson's disease progression, Mov. Disord. 31 (2016) 1535–1542, https://doi.org/10.1002/mds.26754.

[50] D.C. Bäckström, M.E. Domellöf, J. Linder, B. Olsson, A. Öhrfelt, M. Trupp, H. Zetterberg, K. Blennow, L. Forsgren, Cerebrospinal fluid patterns and the risk of future dementia in early, incident Parkinson disease, JAMA Neurol. 72 (2015) 1175–1182, https://doi.org/10.1001/jamaneurol.2015.1449.

[51] T. Yousaf, M. Politis, R. De Micco, H. Wilson, A. Chandra, G. Pagano, REM behavior disorder predicts motor progression and cognitive decline in Parkinson disease, Neurology. 91 (2018) e894–e905, https://doi.org/10.1212/wnl.0000000000006134.

[52] F. Jessen, R.E. Amariglio, M. Van Boxtel, M. Breteler, M. Ceccaldi, G. Chételat, B. Dubois, C. Dufouil, K.A. Ellis, W.M. Van Der Flier, L. Glodzik, A.C. Van Harten, M.J. De Leon, P. McHugh, M.M. Mielke, J.L. Molinuevo, L. Mosconi, R.S. Osorio, A. Perrotin, R.C. Petersen, L.A. Rabin, L. Rami, B. Reisberg, D.M. Rentz, P.S. Sachdev, V. De La Sayette, A.J. Saykin, P. Scheltens, M.B. Shulman, M.J. Slavin, R.A. Sperling, R. Stewart, O. Uspenskaya, B. Vellas, P.J. Visser, M. Wagner, A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease, Alzheimer's Dement. 10 (2014) 844–852, https://doi.org/10.1016/j.jalz.2014.01.001.

[53] J.M. Costerus, M.C. Brouwer, D. van de Beek, Technological advances and changing indications for lumbar puncture in neurological disorders, Lancet Neurol. 17 (2018) 268–278, https://doi.org/10.1016/S1474-4422(18)30033-4.

[54] F.H. Duits, P. Martinez-Lage, C. Paquet, S. Engelborghs, A. Lleó, L. Hausner, J.L. Molinuevo, E. Stomrud, L. Farotti, I.H.G.B. Ramakers, M. Tsolaki, C. Skarsgård, R. Åstrand, A. Wallin, M. Vyhnalek, M. Holmber-Clausen, O.V. Forlenza, L. Ghezzi, M. Ingelsson, E.I. Hoff, G. Roks, A. De Mendonça, J.M. Papma, A. Izagirre, M. Taga, H. Struyfs, D.A. Alcolea, L. Frölich, M. Balasa, L. Minthon, J.W.R. Twisk, S. Persson, H. Zetterberg, W.M. Van Der Flier, C.E. Teunissen, P. Scheltens, K. Blennow, Performance and complications of lumbar puncture in memory clinics: results of the multicenter lumbar puncture feasibility study, Alzheimer's Dement. 12 (2016) 154–163, https://doi.org/10.1016/j.jalz.2015.08.003.

[55] S. Engelborghs, E. Niemantsverdriet, H. Struyfs, K. Blennow, R. Brouns, M. Comabella, I. Dujmovic, W. van der Flier, L. Frölich, D. Galimberti, S. Gnanapavan, B. Hemmer, E. Hoff, J. Hort, E. Iacobaeus, M. Ingelsson, F. Jan de Jong, M. Jonsson, M. Khalil, J. Kuhle, A. Lleó, A. de Mendonça, J.L. Molinuevo, G. Nagels, C. Paquet, L. Parnetti, G. Roks, P. Rosa-Neto, P. Scheltens, C. Skårsgard, E. Stomrud, H. Tumani, P.J. Visser, A. Wallin, B. Winblad, H. Zetterberg, F. Duits, C.E. Teunissen, Consensus guidelines for lumbar puncture in patients with neurological diseases, Alzheimer's Dement, Diagnosis, Assess. Dis. Monit. 8 (2017) 111–126, https://doi.org/10.1016/j.dadm.2017.04.007.

[56] A. Fourier, E. Portelius, H. Zetterberg, K. Blennow, I. Quadrio, A. Perret-Liaudet, Pre-analytical and analytical factors influencing Alzheimer's disease cerebrospinal fluid biomarker variability, Clin. Chim. Acta 449 (2015) 9–15, https://doi.org/10.1016/j.cca.2015.05.024.

[57] P. Lewczuk, A. Matzen, K. Blennow, L. Parnetti, J.L. Molinuevo, P. Eusebi, J. Kornhuber, J.C. Morris, A.M. Fagan, Cerebrospinal fluid Aβ42/40 corresponds better than Aβ42 to amyloid PET in Alzheimer's disease, J. Alzheimers Dis. 55 (2017) 813–822, https://doi.org/10.3233/JAD-160722.

[58] M.G. Spillantini, M.L. Schmidt, V.M.Y. Lee, J.Q. Trojanowski, R. Jakes, M. Goedert, α-synuclein in Lewy bodies [8], Nature. 388 (1997) 839–840, https://doi.org/10.1038/42166.