Clinica Chimica Acta 495 (2019) 318–325

Contents lists available at ScienceDirect

Clinica Chimica Acta

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

Parkinson's and Lewy body dementia CSF biomarkers

Lucilla Parnetti[a,*], Silvia Paciotti[a,b], Lucia Farotti[a], Giovanni Bellomo[c], Federica Nicoletta Sepe[a], Paolo Eusebi[a]

[a] Center for Memory Disturbances, Section of Neurology, Laboratory of Clinical Neurochemistry, Department of Medicine, University of Perugia, Perugia, Italy
[b] Section of Physiology and Biochemistry, Department of Experimental Medicine, University of Perugia, Perugia, Italy
[c] Magnetic Resonance Center (CERM), University of Florence, Sesto Fiorentino, Italy

ARTICLE INFO

Keywords:
Parkinson's disease
Lewy body dementia
Cerebrospinal fluid biomarkers

ABSTRACT

The clinical diagnosis of Parkinson's disease (PD) and Dementia with Lewy bodies (DLB) is challenging due to highly variable clinical presentation and clinical and pathological overlap with other neurodegenerative diseases. Since cerebrospinal fluid (CSF) mirrors the pathological changes taking place in the brain, it represents a promising source of biomarkers.

With respect to classical AD biomarkers, low CSF $A\beta_{42}$ levels have shown a robust prognostic value in terms of development of cognitive impairment in PD and DLB. In the differential diagnosis between AD and DLB, a potential role of t-tau, p-tau and $A\beta_{42}/A\beta_{38}$ ratio has been demonstrated. Regarding CSF α-synuclein (α-syn) species, lower levels of total α-synuclein (t-α-syn) and higher concentration of oligomeric-α-synuclein (o-α-syn) and phosphorylated α-synuclein (p-α-syn) have been observed in PD. Furthermore, the detection of "pro-aggregating" α-synuclein has enabled the discrimination of patients affected by synucleinopathies with high sensitivity and specificity. New promising biomarkers are emerging: GCase activity (reduced in PD and DLB patients vs. controls), CSF/serum albumin ratio (increased in PD and DLB), fatty-acid-binding protein (increased in AD and DLB vs. PD), visinin-like protein-1 (increased in AD vs. DLB) and monoamines (useful in differential diagnosis among PD and DLB). These encouraging results need to be confirmed by future studies.

1. Introduction

Parkinson's Disease (PD) and the closely related Dementia with Lewy bodies (DLB) are due to the accumulation of pathogenic alpha-synuclein (α-syn) in the brain and are characterized by heterogeneous motor and non-motor symptoms, including cognitive impairment. For these common features they belong to the clinical spectrum of Lewy body disorders (LBD). Notably, LBD patients can show pathological heterogeneity, especially for the presence of concomitant Alzheimer's disease (AD) pathology with β-amyloid plaques and neurofibrillary tangles [1].

PD is clinically characterized by the variable presence of core motor symptoms that include bradykinesia, tremor, postural instability and rigidity. It is well known that during the disease course PD patients may develop several degrees of cognitive impairment, from mild cognitive impairment (PD-MCI) [2,3] to Parkinson's disease dementia (PDD) [4].

The presence of motor symptoms and cognitive decline requires an accurate differential diagnosis between PD and various forms of parkinsonism, in particular with DLB, that is the second most common neurodegenerative cause of dementia. According to most recent

Abbreviations: PD, Parkinson's disease; PDD, Parkinson's disease with dementia; MCI, mild cognitive impairment; DLB, dementia with Lewy bodies; LBs, Lewy bodies; AD, Alzheimer's disease; LNs, Lewy neurites; α-syn, α-synuclein; CSF, cerebrospinal fluid; $A\beta_{42}$, amyloid beta peptide; t-tau, total-tau; p-tau, phosphorylated tau; NFT, neurofibrillary tangles; PPMI, Parkinson's Progression Markers Initiative; UPDRS, Parkinson's Disease Rating Scale; MMSE, Mini Mental State Examination; DAT, Dopamine transporter; UPSIT, University of Pennsylvania Smell Identification Test; RBDSQ, REM Sleep Behavior Disorder Screening Questionnaire; 5-HIAA, 5-hydroxyindolacetic acid; MHPG, 3-methoxy-4-hydroxyphenylethylenglycol; MSA, multiple system atrophy; o-α-syn, oligomeric α-synuclein; p-α-syn, phosphorylated α-synuclein; OND, other neurodegenerative disorders; SMD, standard mean difference; HC, healthy controls; CBS, corticobasal syndrome; FTD, frontotemporal dementia; PSP, Progressive supranuclear palsy; CJD, Creutzfeldt-Jakob disease; H&Y, Hoehn & Yahr; TUG, Timed Up and Go; AUC, area under the curve; NfL, neurofilament light chain; RT-QuIC, Real-Time Quaking induced conversion; PMCA, Protein Misfolding cyclic amplification; RBD, rapid eye movement sleep behaviour disorder; GCase, β-glucocerebrosidase; ROC, receiver operating procedures; FABP, fatty acid binding proteins; VILIP-1, visinin-like-protein-1; MoCA, Montreal Cognitive Assessment

* Corresponding author.
E-mail addresses: lucilla.parnetti@unipg.it (L. Parnetti), silvia.paciotti@unipg.it (S. Paciotti), bellomo@cerm.unifi.it (G. Bellomo).

https://doi.org/10.1016/j.cca.2019.04.078
Received 12 November 2018; Received in revised form 24 April 2019; Accepted 24 April 2019
Available online 30 April 2019
0009-8981/

diagnostic criteria, DLB is characterized by the presence of dementia associated with core clinical features such as cognitive fluctuations, visual hallucinations and parkinsonism. If compared to PDD, dementia in DLB usually precedes or coincides with parkinsonism [5]. As in PD, the concept of MCI has been described in DLB, also named prodromal DLB [6].

Since molecular changes in the brain are reflected in the composition of cerebrospinal fluid (CSF), CSF represents an ideal source for biomarkers of different pathophysiological processes characterizing the early phases of the disease, when the clinical diagnosis is more challenging. Thus, the accuracy of differential diagnosis between these neurodegenerative diseases can be implemented by the use of CSF biomarkers, learning from the lesson of AD diagnosis. The aim of this review is to provide an update on PD and DLB CSF biomarkers, focusing on their role in differential diagnosis and prognosis.

2. Methods

The bibliographic search was conducted on Pubmed. Different keywords were typed for this search, such as “Biomarkers AND Parkinson's Disease”, “Biomarkers AND Dementia with Lewy bodies”, “Cerebrospinal fluid AND Parkinson's Disease”, “Cerebrospinal fluid AND Dementia with Lewy bodies”. Both original articles and reviews have been taken into account for the present manuscript.

3. CSF AD biomarkers

AD CSF core biomarkers - the 42 amino acid isoform of amyloid beta ($A\beta_{42}$), total tau (t-tau), phosphorylated tau (p-tau) - reflect key aspects of the disease pathogenesis, i.e. aggregation and deposition of $A\beta_{42}$ into plaques, neuronal degeneration and phosphorylation of tau with neurofibrillary tangles (NFTs) formation. In AD, the typical CSF profile is characterized by reduced CSF $A\beta_{42}$ and increased t-tau and p-tau levels [7]. Amyloid plaques and NFTs have been observed in approximately 40% of patients affected by PD, PD with dementia and DLB, thus leading to assess the role of CSF AD biomarkers in the diagnosis of LBD [8].

No significant differences of CSF $A\beta_{42}$ were found when PD patients were compared with controls subjects [9–11]. Recently, Parkinson's Progression Markers Initiative (PPMI) multicentric study enrolled 173 naive PD patients measuring CSF α-syn, $A\beta_{42}$, p-tau and t-tau levels at baseline and at 6- and 12-month follow-up visits [12]. In the PD group there was a small but significant increase in CSF $A\beta_{42}$ and p-tau from baseline to follow-up. T-tau and α-syn concentrations remained relatively stable. No correlation was found with changes in the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale motor scores (UPDRS-III) or dopamine imaging. CSF a-syn levels at 12 months were lower in PD patients treated with dopamine agonists than controls.

In PD patients, the prognostic value of CSF AD biomarkers was also investigated in terms of development of cognitive impairment and dementia. According to available data, low CSF $A\beta_{42}$ levels have a robust prognostic value in terms of development of cognitive decline in PD. A total of 45 patients with PD were enrolled in a prospective cohort study: CSF was collected at baseline, cognition was assessed at baseline and during the follow-up. Reduced CSF $A\beta_{42}$ was an independent predictor of cognitive decline, while CSF t-tau and p-tau levels were not significantly associated with cognitive outcome [13]. Similarly, in a prospective study carried out in 44 PD patients and 25 controls, lower CSF $A\beta_{42}$ levels were associated with a higher rate of Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) decline, confirming its role as independent predictive factor for cognitive impairment [11]. Data from 341 PD patients enrolled in the PPMI cohort [14] suggested that those presenting cognitive impairment at a 2-year-follow-up had significantly lower baseline CSF $A\beta_{42}$ levels than those who did not.

Findings for t-tau and p-tau are not consistent with a clear prognostic value in PD, unlike $A\beta_{42}$. longitudinal studies showed that CSF t-tau levels measured at baseline were not predictive of cognitive decline in PD [13]. Only two longitudinal studies found a significant association with p-tau and the rate of cognitive decline [15,16]. Reduced CSF $A\beta_{42}$ levels at baseline seemed to be an independent predictor of development of early L-dopa-resistant gait impairment [17] and psychosis [18]. In a multivariate analysis in 2017, in a population of 390 newly diagnosed PD from a PPMI cohort, five variables showed the most significant associations with the development of cognitive impairment (age, UPSIT, RBDSQ, CSF $A\beta_{42}$ levels and caudate uptake on DAT imaging) at a 2 year follow-up (AUC = 0·80, 95% CI 0·74–0·87; p = 0·0003 compared to age alone) [19].

Results from CSF biomarkers studies confirm the relevant role of AD pathology also in DLB, similarly to what observed in PD. Results from a Large Multicenter Cohort including 594 patients with a clinical diagnosis of probable DLB, PDD and PD confirmed this hypothesis, showing a CSF profile compatible with AD (low $A\beta_{42}$ combined with high t-tau and/or p-tau) in almost 25% of DLB patients, compared with only 9% of the PDD patients and 3% of the PD patients. Within DLB, patients with a CSF AD profile performed worse on MMSE [20].

Classical AD CSF biomarkers have been explored also as potential differential diagnosis tools in DLB patients. In a study led by Parnetti and Tiraboschi in 2008 [21], CSF $A\beta_{42}$, t-tau and p-tau levels were assessed in a cohort of patients with a clinical diagnosis of PD, PDD, DLB and AD and of age-matched, cognitively normal subjects. DLB showed the lowest mean CSF $A\beta_{42}$ concentration, with a negative association to dementia duration. In DLB patients, mean CSF t-tau levels were significantly lower than in AD patients, but higher than in PDD or controls, with a positive association to dementia severity. P-tau levels were significantly increased in the AD group only, which is consistent with a more relevant presence of NFTs. Some studies substantially confirmed these results [22], whereas others did not. For example, in Bibl et al., tau levels resulted significantly elevated and $A\beta_{42}$ significantly reduced in AD patients as compared to the DLB group [23]. Finally, some studies indicated not statistically significant differences in $A\beta_{42}$ levels of DLB patients compared to those of AD patients, with tau species significantly higher in AD [24,25].

Among the various explanations of these conflicting results, clinical factors such as disease stage should be taken into account. An interesting retrospective study included 1221 CSF samples of AD and DLB patients (both at prodromal and dementia stages) and controls showing that in prodromal DLB $A\beta_{42}$ levels were much less altered than in DLB patients at the demented stage, where levels reached those of patients with AD. Unlike AD, the $A\beta_{42}/A\beta_{40}$ ratio in patients with prodromal DLB remained close to controls, and t-tau and p-tau were unaltered in patients with DLB [26]. Furthermore, in a study carried out on 30 patients diagnosed as AD, 23 DLB, 20 PDD and 12 non-demented control subjects, the $A\beta_{42}/A\beta_{38}$ ratio was the strongest marker for differentiation between AD and DLB, suggesting a role of $A\beta_{38}$ in the differential diagnosis [27].

Finally, the prognostic value of CSF biomarkers in DLB has been evaluated in a prospective study, that analysed baseline AD CSF biomarkers of 100 DLB patients annually evaluated for up to 2 years, in which the AD CSF profile and pathological levels of $A\beta_{42}$ were associated with a more rapid decline in MMSE. Higher t-tau values showed a trend toward association, even if without statistical significance, while p-tau was not associated with decline [28].

4. The issue of α-synuclein

α-syn is a 140 residues protein highly expressed in the central nervous system [29,30] and mainly present at the presynaptic neuronal terminals. The physiological role carried out by this protein is still largely unknown, however it seems to be involved in the regulation of neurotransmitter release, synaptic plasticity and vesicle trafficking,

brain lipid metabolism and remodelling of the membranes [31–34]. At cellular level, α-syn is predominantly present as unfolded soluble monomer with not well-defined secondary or tertiary structures [35–37]. Several factors interfering with α-syn proteostasis [35,36,38–47] can promote the misfolding of α-syn with the consequent formation of oligomers and amyloid-like fibrils rich in cross β-sheet secondary structures [48,49]. α-syn is the major constituent of LBs and LNs, which are considered the main histopathological hallmarks of PD and DLB [50,51]; aggregated α-syn is also found in oligodendrocytes of patients affected by multiple system atrophy (MSA), where it forms glial cytoplasmic inclusions [50–55].

Several studies have confirmed the central role played by α-syn in the development of PD and other synucleinopathies and led to investigate the diagnostic value of different α-syn species, i.e. total-α-syn (t-α-syn), oligomeric-α-syn (o-α-syn), phosphorylated-α-syn at Serine 129 (p-α-syn) and "pro-aggregating" α-syn, as biomarkers of synucleinopathies [56–58]. Recently, a meta-analysis performed by Eusebi et al. [59], confirmed the significantly lower CSF t-α-syn levels and the higher CSF concentration of both o-α-syn and p-α-syn in PD with respect to controls, already described by other meta-analyses [60,61]. Regarding t-α-syn, 32 studies published between 2008 and 2016, including 2070 PD patients and 1428 controls, were selected as eligible for meta-analyses. Concentration of t-α-syn was significantly lower in PD compared to both healthy controls (HC) (17 studies) and controls affected by neurological disorders (OND) (15 studies). An average standard mean difference (SMD) [59] of t-α-syn of −0.51 with a 95% confidence interval (CI) of [−0.65;-0.37] ($p < 0.001$) was found for PD vs. HC and a SMD of −0.45 with a 95% CI of [−0.68;-0.22] ($p < 0.001$) was found vs. OND. The overall SMD of PD versus both OND and HC was found to be −0.48 with a 95% CI of [−0.60;-0.36]. On 8 studies eligible for o-α-syn (345 PD patients and 255 controls) and 2 studies eligible for p-α-syn (114 controls and 96 PD patients) an overall SMD of 0.57 with a 95% CI of [0.34;0.79] ($p < 0.001$) for o-α-syn distinguishing PD vs. controls and a SMD of 0.86 with a 95% CI of [0.54; 1.18] ($p < 0.001$) for p-S129-α-syn were observed.

In the context of differential diagnosis among synucleinopathies, CSF t-α-syn is found to be similar between PD and DLB [59,62,63]. CSF t-α-syn is not found to be significantly different neither between PD and MSA patients [59–61], even though a meta-analysis reported significantly higher levels of CSF t-α-syn in PD with respect to MSA [64]. Although CSF t-α-syn does not seem to produce good differentiation among synucleinopathies it was found to be significantly higher in AD [61,63] and Creutzfeldt-Jakob disease (CJD) [61,65] with respect to PD, DLB, MSA and controls, showing possible applications as an unspecific synaptic degeneration marker.

Regarding the possible use of α-syn species as prognostic markers, different studies gave contrasting results. Some reports showed a positive association between t-α-syn and Hohen&Yahr (H&Y) stage, UPDRS-III, and prolonged Timed Up and Go (TUG) test over 2 years [66], as well as the ability of low CSF t-α-syn to predict motor progression [67]. However, in other studies no significant association between baseline CSF t-α-syn and subsequent motor progression was found [15,68,69]. Also the value of t-α-syn as prognostic marker of cognitive impairment was not clear. Some studies reported higher CSF t-α-syn levels associated with the worsening of cognitive functions [66,70] and low CSF t-α-syn as a significant predictor of cognitive decline in PD [67], whereas in other studies no prognostic effect of CSF α-syn species was observed [15,68,69,71].

It has been shown that the combination of α-syn species among one another or with other CSF biomarkers can improve their diagnostic performance. Two different studies reported that the CSF o-α-syn/t-α-syn ratio was able to discriminate PD vs. controls with an area under the curve (AUC) of 0.79 (sensitivity = 0.65, specificity = 0.83) [67] and 0.82 (sensitivity = 0.68, specificity = 0.85) [72], respectively. In 2014, Hansson et al. [73] highlighted the fact that o/t-α-syn ratio could distinguish DLB or PDD patients from AD patients, with AUC of 0.64 and 0.75, respectively. In addition, t-α-syn alone could distinguish DLB or PDD patients from AD patients, with an AUC of 0.80.

In 2011 Mollenhauer et al. [74] showed that a similar decrease in $A\beta_{40}$ and $A\beta_{42}$ links DLB and AD suggesting that AD biomarkers could help in the diagnosis of DLB. In 2016, also Llorens et al. [75] confirmed this hypothesis showing that the t-tau/t-α-syn ratio produced good clinical accuracy in discriminating controls from DLB (AUC = 0.8776) compared to single t-α-syn (AUC = 0.7192) and t-tau (AUC = 0.7739). Moreover, also another recent study [76] showed that α-syn species combined with AD biomarkers are good predictors for DLB. In this study, models based on multiple logistic regression showed that the combination of o-α-syn and t-tau can differentiate DLB (41 subjects) from AD (35 subjects) with a sensitivity of 81% and a specificity of 74%, the combination of age, sex, o-α-syn, t-α-syn, $A\beta_{42}$ and t-tau differentiates DLB from controls (78 subjects) with a sensitivity of 68% and a specificity of 93% and the combinations of sex, t-tau and $A\beta_{42}$ differentiates between DLB from PD (46 subjects) with a sensitivity of 85% and a specificity of 79%. Furthermore, the combination of CSF α-syn species with the AD core biomarkers further increased the diagnostic accuracy in discriminating PD vs. controls [77–79] and their combination with the neurofilament light chain protein (NfL) was able to discriminate PDD and DLB vs. AD (AUC = 90%, sensitivity = 90%, specificity = 81%) and PD vs PSP, MSA and CBS (AUC = 93%, sensitivity = 85%, specificity = 92%) [80].

Recently, two novel ultrasensitive protein amplification assays, named Protein-Misfolding Cyclic Amplification (PMCA) and Real-Time Quaking-Induced Conversion (RT-QuIC), were applied for the detection of "pro-aggregating" α-syn in CSF [81]. In 2016, Fairfoul et al. [82] reported the first application of RT-QuIC on CSF samples of patients affected by synucleinopathies and controls obtaining a sensitivity of 95% for PD (102 PD CSF and 35 controls) and 92% for DLB (15 DLB CSF and 3 controls) with both specificities of 100% with respect to HC and AD patients. Interestingly, RT-QuIC showed also the potential to diagnose synucleinopathies in a pre-symptomatic phase, since it was able to detect aggregates in CSF samples of patients affected by rapid eye movement sleep behaviour disorder (RBD) who developed synucleinopathies a few years later. In 2017, Shahnawaz et al. [83] discriminated PD, MSA and DLB patients from OND with a sensitivity of 88.5%, 80% and 100% and a specificity of 94% respectively. Notably, some control subjects which had a positive response for α-syn PMCA developed a synucleinopathy years after undergoing the lumbar puncture. By considering these subjects, the recalculated specificity was of 96.9%. In 2018, Groveman et al. [84] performed a blinded analysis of CSF from 29 synucleinopathy cases (12 PD and 17 DLB) and 31 non-synucleinopathy controls, including 16 AD cases, which yielded a sensitivity of 93% and specificity of 100%.

Despite the good performance given by RT-QuIC and α-syn PMCA, it is important to note that neither PMCA nor RT-QuIC, are currently able to discriminate among different synucleinopathies, thus more indepth investigations on the α-syn aggregation kinetics as well as on the structure of the α-syn fibrillary aggregates should be done for this purpose [85–89].

5. Other biomarkers

5.1. GCase activity

Reduced activity of the autophagic-lysosomal system is generally associated with intracellular protein accumulation and it is an early event in pathogenesis of synucleinopathies [90–92].

Two large multicentre studies on PD and DLB patients defined mutations on the GBA gene, enconding for the lysosomal enzyme β-glucocerebrosidase (GCase), the most common genetic risk factor involved in the development of these disorders, suggesting that genetic variants of the GBA gene contribute to pathogenesis of synucleinopathies [93,94]. Particularly, GBA mutation carriers show a 20-fold

increased risk to develop PD and 9-fold increased risk of developing DLB as compared to non-carriers [95].

During the last ten years a few studies investigated the possible role of CSF GCase activity as biomarkers for PD. Most of them showed significantly reduced GCase activity in PD patients with respect to both healthy and neurological controls [96–98]. However, the diagnostic accuracy of CSF GCase activity alone in discriminating PD from controls was suboptimal. Two studies reported a significant improvement of diagnostic performance combining CSF GCase activity with either CSF o-α-syn/t-α-syn ratio and age (sensitivity 82% and specificity 71%) [96] or with the CSF activities of other lysosomal enzymes (namely Cathepsin D and β-hexosaminidase) and the $A\beta_{42}$ and t-α-syn levels (sensitivity 84% and specificity 75%) [98]. It is worth to note that the reduction of CSF GCase activity in PD patients seems to be independent from the presence of mutations on the GBA gene as indicated by Parnetti and colleagues [98]. The same authors reported a significant association between reduced CSF GCase activity and worse cognitive performance assessed by MoCA score ($r = 0.26$, $p < 0.047$) and a significant correlation between lower CSF GCase activity and PD progression.

Regarding the CSF GCase activity in DLB patients, only one study investigated this issue in a small Italian cohort [99]. GCase activity was significantly lower in DLB patients with respect to patients affected by AD, FTD and neurological controls, thus suggesting a specific involvement of GCase in α-syn homeostatic processes.

5.2. CSF/serum albumin ratio

The CSF/serum albumin ratio represents the best-established biomarker for the integrity of the blood-brain barrier (BBB) and corresponds to the ratio of the albumin concentration in CSF to serum. Albumin is only synthesized in liver, thus the increase of CSF/serum albumin ratio indicates altered permeability of the BBB.

CSF/serum albumin seems to increase in patients affected by PD and DLB [100–102]. Pisani et al. [100], investigated the CSF/serum albumin ratio in 73 non-demented PD patients ($n = 46$ with H&Y staging between 1 and 2 and $n = 27$ with a score ranging from 2.5 to 4), 11 subjects with no neurological diseases and 47 age-matched controls. A significant difference in CSF/serum albumin ratio ($P = 0.02$) was found between PD and controls. CSF/serum albumin ratio was significantly higher in patients at the advanced stage of the disease with respect to early stage patients ($p = 0.002$), neurological disease controls ($p < 0.01$) and healthy controls ($p < 0.001$). Conversely, no difference was found between early-phase patients and control groups.

In another study performed by Janelizde et al. [101] involving a cohort of non-demented PD patients ($n = 82$), patients affected by PDD ($n = 18$) and controls ($n = 38$), the CSF/plasma albumin ratio differed between the diagnostic groups ($p < 0.005$). The ratio was higher in non-demented PD patients ($p < 0.001$) and PDD patients ($p < 0.027$) compared to controls, while no difference was found between non-demented PD and PDD. Finally, Llorens et al. [102] explored the potential role of the CSF/plasma albumin ratio as a biomarker in the differential diagnosis of neurological diseases including depression, epilepsy, encephalitis, stroke, normal pressure hydrocephalus, vascular dementia, MCI, AD, FTD, CJD, PD, PDD, DLB and controls. The CSF/plasma albumin ratio increased in DLB cases compared to other neurological and neurodegenerative diseases ($p < 0.001$) and to PDD cases ($p < 0.05$). A ROC analysis showed that the CSF/plasma albumin ratio was significantly different between DLB vs. controls (AUC = 0.85, $p < .0001$), DLB vs. PD (AUC = 0.79, $p < 0.0001$) and DLB vs. PDD (AUC = 0.68, $p < 0.038$). It is worth to note that in PDD the CSF/plasma albumin ratio was significantly increased compared to control cases ($p < 0.01$); no difference was detected between control and PD cases. Interestingly, in DLB the CSF/plasma albumin ratio was significantly different to that detected in non-dementia and dementia cases. A receiver characteristic curve (ROC) analysis demonstrated that the CSF/plasma albumin ratio was able to discriminate DLB cases from non-dementia and dementia patients (non-dementia vs. DLB, AUC = 0.81; dementia vs. DLB, AUC = 0.81). Finally, the combination of CSF/plasma albumin ratio and the CSF $A\beta_{42}$ levels significantly increases the discriminatory potential between DLB and PD/PDD (AUC = 0.84 for PD vs. DLB and AUC = 0.80 for PDD vs. DLB).

5.3. Fatty acid binding protein 3

Brain lipids play a fundamental role in central nervous system physiology [103]. The intracellular transport of fatty acids, cholesterol and retinoids is facilitated by fatty acid binding proteins (FABPs), a multigene family of small lipid-binding proteins, widely expressed in mammalian tissues [104]. Among FABPs, FABP3 has been linked to the molecular mechanisms of neurodegeneration and has been also proposed as candidate biomarker, due to its increased levels in the CSF of patients with AD, PDD, DLB and VaD [105]. In AD patients this analyte seems to be a useful CSF biomarker predictive of the conversion to dementia in a patient with cognitive decline or MCI due to AD [106] and for differential diagnosis with other neurodegenerative diseases such as DLB [63]. Likewise for AD, CSF FABP3 levels seem to be predictive for developing dementia in patients with PD-MCI [68]. CSF levels of FABP3, NfL, $A\beta_{42}$, t-tau, p-tau and t-α-syn were quantified at baseline and after 1 year and compared with the CSF results from 30 healthy control participants. In PD, high NfL, low $A\beta_{42}$ and high FABP3 at baseline were significantly associated with the development of dementia [68]. Recently, our group performed a prospective study in a large cohort of patients ($n = 208$) to evaluate CSF FABP3 performance in differentiating between AD, PDD, DLB, PD and neurological controls. FABP3 levels were significantly increased in patients with AD and DLB compared with those with PD and controls. Additionally, the combination of FABP3 with p-tau showed high accuracy in differentiating between AD and DLB, while the combination of p-tau, FABP3 and α-syn better discriminated between AD and PDD patients [63].

5.4. Visinin like protein-1

Visinin-like protein-1 (VILIP-1) is a member of the neuronal calcium sensor protein family and has been proposed [107] as a new biomarker, expression of calcium-mediated neurodegeneration in AD and other neurodegenerative disorders. Braunewell proposed a mechanism by which Aβ deposition leads to deregulation of calcium homeostasis in AD [108]. In this model, Aβ directly modulates the expression of neuronal calcium sensor proteins downregulating VILIP-1. This imbalance of calcium sensor and buffer proteins ratio makes neurons more vulnerable to Aβ-induced calcium-mediated neurotoxicity, as Aβ induces the release of calcium from internal sarcoplasmic reticulum and enhances external calcium influx. These factors might contribute to neuronal cell death and to the increase of VILIP-1 in CSF and plasma in AD patients [109–111]. Recent studies showed that CSF VILIP-1 levels increased in patients with MCI due to AD compared with controls and decreased during the course of the disease [112], thus representing a predictive biomarker of cognitive decline [113]. Importantly, CSF VILIP-1 could be useful in the differential diagnosis of AD with other forms of dementia as DLB. In a cohort composed by 61 AD patients, 32 DLB patients, and 40 healthy controls levels of CSF VILIP- 1, t-Tau, p-Tau, $A\beta_{42}$, and t-α-syn were measured. CSF VILIP-1 levels were significantly increased in AD patients compared with both controls and DLB with sensitivity and specificity of 78.7% and 87.5%, respectively [113].

5.5. Monoamines

In central nervous system, biogenic amines, such as noradrenaline (NA), dopamine (DA) and serotonin (5- hydroxytryptamine; 5-HT) play a crucial role in memory processes, cognitive decline and behavioral

symptoms in neurodegenerative disorders [114–117]. Notably, CSF levels of NA resulted increased in patients with advanced AD, suggesting hyperactivity of the noradrenergic system in the final stages of the disease [118]. Furthermore, the locus coeruleus (LC), the main NA-producing nucleus in the brain, is severely affected by Lewy pathology in PD and DLB and neurodegeneration in this nucleus induces severe apoptosis of dopaminergic nigrostriatal neurons in substantia nigra through loss of noradrenergic innervation [119]. For this reason, monoamines and their metabolites may play an important role in the differential diagnosis among several neurodegenerative diseases.

Recently, Janssen and colleagues, detected the diagnostic accuracy of a panel composed by the combination of monoamine and relative metabolite levels and core AD biomarkers in CSF and serum in a population composed by 52 AD, 59 FTD, 39 DLB, 4 PDD and 88 controls. CSF 3-methoxy-4-hydroxyphenylglycol (MHPG) levels, one of the main NA metabolites, resulted higher, whereas serum levels were lower, in DLB/PDD compared with all other groups, increasing diagnostic accuracy between LBD and AD [120].

Also a Dutch group investigated whether CSF monoamine levels in addition to classical AD biomarkers, would improve the differentiation between DLB and AD. CSF concentrations of homovanillic acid (HVA), 5- hydroxyindolacetic acid (5-HIAA), and MHPG, all catabolic end-products of dopamine and epinephrine degradation, as well as those for t-tau and p-tau protein, resulted significantly lower in DLB than in AD. The highest diagnostic accuracy was reached by combining MHPG and the classical AD biomarkers [121].

Moreover, in LBD, CSF and serum monoamines could be considered as potential stage markers. Indeed, CSF and serum monoamine levels resulted to correlate to dementia status in a cohort composed by 28 PD with normal cognition (PD-NC), 26 PD-MCI, 18 PDD, 38 DLB and 43 healthy controls (HC). CSF MHPG levels grew in a progressive manner from HC to PDD/DLB patients, increasing with cognitive decline. Interestingly, CSF 5-hydroxyindoleacetic acid (5-HIAA) levels, an adrenergic system metabolite, was the most discriminative parameter to differentiate HC from other groups with the exception of PD-NC [122].

6. Conclusions

Since in clinical setting diagnosis of PD and DLB remains challenging because of their heterogeneity and clinical overlap with other neurological disorders, reliable biomarkers are needed. This issue becomes even more important when dealing with the disease at an early stage.

Recently, several multicentre studies have contributed to improve our knowledge on the field of CSF biomarkers and promising results were obtained combining biomarkers reflecting the pathophysiological mechanisms occurring along the disease course. However, longitudinal studies, reflecting the prodromal and clinical continuum of these disorders, are still required to clarify the diagnostic accuracy, the reliability and the predictability of the CSF biomarkers. $A\beta_{42}$ revealed a significant role as predictor of cognitive impairment both in DLB and PD, encouraging the use of AD biomarkers in clinical practice. α-syn is the pathological hallmark of PD and DLB, carrying out a key role in their pathogenesis; however, reliable biomarkers are still lacking. In this setting, lower levels of t-α-syn and higher concentration of o-α-syn have been observed in PD and DLB. Furthermore, the detection of “pro-aggregating” α-syn species in CSF seems to have the potential to diagnose patients affected by synucleinopathies in asymptomatic phase. Standardization of analytical techniques and generation of reference materials will fill the gap between research and clinical setting, learning from the lesson of AD. Over the last years, many new molecules have been proposed as biomarker candidates, referring to different pathophysiological mechanisms. Their combination with AD biomarkers and α-syn species could be the most promising panel for differential diagnosis and prognosis. Further studies are needed to provide more details on this issue.

Acknowledgments

The work of Paolo Eusebi was supported by the Italian Ministry of Health (Grant GR-2013-02357757).

References

[1] M. Colom-Cadena, O. Grau-Rivera, L. Planellas, C. Cerquera, E. Morenas, S. Helgueta, L. Munoz, J. Kulisevsky, M.J. Marti, E. Tolosa, J. Clarimon, A. Lleo, E. Gelpi, Regional overlap of pathologies in lewy body disorders, J. Neuropathol. Exp. Neurol. (2017), https://doi.org/10.1093/jnen/nlx002.
[2] D. Aarsland, K. Bronnick, C. Williams-Gray, D. Weintraub, K. Marder, J. Kulisevsky, D. Burn, P. Barone, J. Pagonabarraga, L. Allcock, G. Santangelo, T. Foltynie, C. Janvin, J.P. Larsen, R.A. Barker, M. Emre, Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis, Neurology (2010), https://doi.org/10.1212/WNL.0b013e3181f39d0e.
[3] I. Litvan, D. Aarsland, C.H. Adler, J.G. Goldman, J. Kulisevsky, B. Mollenhauer, M.C. Rodriguez-Oroz, A.I. Tröster, D. Weintraub, MDS task force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI, Mov. Disord. (2011), https://doi.org/10.1002/mds.23823.
[4] M. Emre, D. Aarsland, R. Brown, D.J. Burn, C. Duyckaerts, Y. Mizuno, G.A. Broe, J. Cummings, D.W. Dickson, S. Gauthier, J. Goldman, C. Goetz, A. Korczyn, A. Lees, R. Levy, I. Litvan, I. McKeith, W. Olanow, W. Poewe, N. Quinn, C. Sampaio, E. Tolosa, B. Dubois, Clinical diagnostic criteria for dementia associated with Parkinson's disease, Mov. Disord. (2007), https://doi.org/10.1002/mds.21507.
[5] I.G. McKeith, et al., Diagnosis and management of dementia with Lewy bodies. Fourth consensus of the DLB consortium, Neurology (2017), https://doi.org/10.1212/01.wnl.0000187889.17253.b1.
[6] P.C. Donaghy, I.G. McKeith, The clinical characteristics of dementia with Lewy bodies and a consideration of prodromal diagnosis, Alzheimers Res. Ther. (2014), https://doi.org/10.1186/alzrt274.
[7] 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, Alzheimers Dement. 14 (2018) 535–562, https://doi.org/10.1016/j.jalz.2018.02.018.
[8] D.J. Irwin, S.X. Xie, D. Coughlin, N. Nevler, R.S. Akhtar, C.T. McMillan, E.B. Lee, D.A. Wolk, D. Weintraub, A. Chen-Plotkin, J.E. Duda, M. Spindler, A. Siderowf, H.I. Hurtig, L.M. Shaw, M. Grossman, J.Q. Trojanowski, CSF tau and β-amyloid predict cerebral synucleinopathy in autopsied Lewy body disorders, Neurology (2018), https://doi.org/10.1212/WNL.0000000000005166.
[9] L. Parnetti, D. Chiasserini, G. Bellomo, D. Giannandrea, C. De Carlo, M.M. Qureshi, M.T. Ardah, S. Varghese, L. Bonanni, B. Borroni, N. Tambasco, P. Eusebi, A. Rossi, M. Onofrj, A. Padovani, P. Calabresi, O. El-Agnaf, Cerebrospinal fluid Tau/α-synuclein ratio in Parkinson's disease and degenerative dementias, Mov. Disord. 26 (2011) 1428–1435, https://doi.org/10.1002/mds.23670.
[10] H. Přikrylová Vranová, J. Mareš, M. Nevrlý, D. Stejskal, J. Zapletalová, P. Hluštík, P. Kaňovský, CSF markers of neurodegeneration in Parkinson's disease, J. Neural Transm. 117 (2010) 1177–1181, https://doi.org/10.1007/s00702-010-0462-z.
[11] 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. 6 (2014) 53, https://doi.org/10.3389/fnagi.2014.00053.
[12] B. Mollenhauer, C.J. Caspell-Garcia, M.S. Christopher Coffey, P. Taylor, S.M. Leslie Shaw, J.Q. Trojanowski, A. Singleton, M. Frasier, K. Marek, D. Galasko, Longitudinal CSF biomarkers in patients with early Parkinson disease and healthy controls, Neurology 89 (2017) 1959–1969, https://doi.org/10.1212/WNL.0000000000004609.
[13] 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 1-42 predicts cognitive decline in Parkinson disease, Neurology 75 (2010) 1055–1061, https://doi.org/10.1212/WNL.0b013e3181f39a78.
[14] M. Terrelonge, K.S. Marder, D. Weintraub, R.N. Alcalay, CSF ??-amyloid 1-42 predicts progression to cognitive impairment in newly diagnosed Parkinson disease, J. Mol. Neurosci. 58 (2016) 88–92, https://doi.org/10.1007/s12031-015-0647-x.
[15] 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.
[16] C. Liu, B. Cholerton, M. Shi, C. Ginghina, K.C. Cain, P. Auinger, J. Zhang, CSF tau and tau/Aβ42predict cognitive decline in Parkinson's disease, Park. Relat. Disord. (2015), https://doi.org/10.1016/j.parkreldis.2014.12.027.
[17] 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 88 (2017) 1501–1511, https://doi.org/10.1212/WNL.0000000000003840.
[18] 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 (2017), https://doi.org/10.1136/jnnp-2016-314832.
[19] A. Schrag, U.F. Siddiqui, Z. Anastasiou, D. Weintraub, J.M. Schott, Clinical variables and biomarkers in prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease: a cohort study, Lancet Neurol. 16 (2016) 66–75, https://doi.org/10.1016/S1474-4422(16)30328-3.
[20] I. van Steenoven, D. Aarsland, D. Weintraub, E. Londos, F. Blanc, W.M. van der Flier, C.E. Teunissen, B. Mollenhauer, T. Fladby, M.G. Kramberger, L. Bonanni, A.W. Lemstra, European DLB consortium, Cerebrospinal fluid Alzheimer's disease biomarkers across the Spectrum of Lewy body diseases: results from a large Multicenter cohort, J. Alzheimers Dis. 54 (2016) 287–295, https://doi.org/10.3233/JAD-160322.
[21] 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.
[22] 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. (2014), https://doi.org/10.3233/JAD-130995.
[23] 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. (2006), https://doi.org/10.1007/s00702-006-0537-z.
[24] 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.
[25] 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 (2010), https://doi.org/10.1136/jnnp.2009.197483.
[26] 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 89 (2018) 467–475, https://doi.org/10.1136/jnnp-2017-316385.
[27] E. Mulugeta, E. Londos, C. Ballard, G. Alves, H. Zetterberg, K. Blennow, R. Skogseth, L. Minthon, D. Aarsland, CSF amyloid β38 as a novel diagnostic marker for dementia with Lewy bodies, J. Neurol. Neurosurg. Psychiatry 82 (2011) 160–164, https://doi.org/10.1136/jnnp.2009.199398.
[28] 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), https://doi.org/10.1002/mds.26668.
[29] R. Jakes, M.G. Spillantini, M. Goedert, Identification of two distinct synucleins from human brain, FEBS Lett. 345 (1994) 27–32, https://doi.org/10.1016/0014-5793(94)00395-5.
[30] K.J. Spinelli, J.K. Taylor, V.R. Osterberg, M.J. Churchill, E. Pollock, C. Moore, C.K. Meshul, V.K. Unni, Presynaptic α-synuclein aggregation in a mouse model of Parkinson's disease, J. Neurosci. 34 (2014) 2037–2050, https://doi.org/10.1523/JNEUROSCI.2581-13.2014.
[31] L. Maroteaux, R.H. Scheller, The rat brain synucleins; family of proteins transiently associated with neuronal membrane, Brain Res. Mol. Brain Res. 11 (1991) 335–343.
[32] O. Marques, T.F. Outeiro, Alpha-synuclein: from secretion to dysfunction and death, Cell Death Dis. 3 (2012) e350, https://doi.org/10.1038/cddis.2012.94.
[33] J. Varkey, J.M. Isas, N. Mizuno, M.B. Jensen, V.K. Bhatia, C.C. Jao, J. Petrlova, J.C. Voss, D.G. Stamou, A.C. Steven, R. Langen, Membrane curvature induction and Tubulation are common features of Synucleins and Apolipoproteins, J. Biol. Chem. 285 (2010) 32486–32493, https://doi.org/10.1074/jbc.M110.139576.
[34] D. Ottolini, T. Calí, I. Szabò, M. Brini, Alpha-synuclein at the intracellular and the extracellular side: functional and dysfunctional implications, Biol. Chem. 398 (2017) 77–100, https://doi.org/10.1515/hsz-2016-0201.
[35] M. Hashimoto, L.J. Hsu, Y. Xia, A. Takeda, A. Sisk, M. Sundsmo, E. Masliah, Oxidative stress induces amyloid-like aggregate formation of NACP/α- synuclein in vitro, Neuroreport 10 (1999) 717–721, https://doi.org/10.1097/00001756-199903170-00011.
[36] P.H. Weinreb, W. Zhen, A.W. Poon, K.A. Conway, P.T. Lansbury, NACP, a protein implicated in Alzheimer's disease and learning, is natively unfolded, Biochemistry 35 (1996) 13709–13715, https://doi.org/10.1021/bi961799n.
[37] F.-X. Theillet, A. Binolfi, B. Bekei, A. Martorana, H.M. Rose, M. Stuiver, S. Verzini, D. Lorenz, M. van Rossum, D. Goldfarb, P. Selenko, Structural disorder of monomeric α-synuclein persists in mammalian cells, Nature 530 (2016) 45–50, https://doi.org/10.1038/nature16531.
[38] R.J. Perrin, W.S. Woods, D.F. Clayton, J.M. George, Exposure to long chain polyunsaturated fatty acids triggers rapid multimerization of synucleins, J. Biol. Chem. 276 (2001) 41958–41962, https://doi.org/10.1074/jbc.M105022200.
[39] R. Sharon, I. Bar-Joseph, M.P. Frosch, D.M. Walsh, J.A. Hamilton, D.J. Selkoe, The formation of highly soluble oligomers of alpha-synuclein is regulated by fatty acids and enhanced in Parkinson's disease, Neuron 37 (2003) 583–595.
[40] I. Lonskaya, N.M. Desforges, M.L. Hebron, C.E.H. Moussa, Ubiquitination increases parkin activity to promote autophagic a-synuclein clearance, PLoS One 8 (2013), https://doi.org/10.1371/journal.pone.0083914.
[41] T.A. Thibaudeau, R.T. Anderson, D.M. Smith, A common mechanism of proteasome impairment by neurodegenerative disease-associated oligomers, Nat. Commun. 9 (2018), https://doi.org/10.1038/s41467-018-03509-0.
[42] D. Ruzafa, Y.S. Hernandez-Gomez, G. Bisello, K. Broersen, B. Morel, F. Conejero-Lara, The influence of N-terminal acetylation on micelle-induced conformational changes and aggregation of α-Synuclein, PLoS One 12 (2017) e0178576, , https://doi.org/10.1371/journal.pone.0178576.
[43] G. Andringa, K.Y. Lam, M. Chegary, X. Wang, T.N. Chase, M.C. Bennett, Tissue transglutaminase catalyzes the formation of alpha-synuclein crosslinks in Parkinson's disease, FASEB J. 18 (2004) 932–934, https://doi.org/10.1096/fj.03-0829fje.
[44] K.E. Paleologou, A. Oueslati, G. Shakked, C.C. Rospigliosi, H.-Y. Kim, G.R. Lamberto, C.O. Fernandez, A. Schmid, F. Chegini, W.P. Gai, D. Chiappe, M. Moniatte, B.L. Schneider, P. Aebischer, D. Eliezer, M. Zweckstetter, E. Masliah, H.A. Lashuel, Phosphorylation at S87 is enhanced in synucleinopathies, inhibits alpha-synuclein oligomerization, and influences synuclein-membrane interactions, J. Neurosci. 30 (2010) 3184–3198, https://doi.org/10.1523/JNEUROSCI.5922-09.2010.
[45] W. Li, N. West, E. Colla, O. Pletnikova, J.C. Troncoso, L. Marsh, T.M. Dawson, P. Jäkälä, T. Hartmann, D.L. Price, M.K. Lee, Aggregation promoting C-terminal truncation of alpha-synuclein is a normal cellular process and is enhanced by the familial Parkinson's disease-linked mutations, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 2162–2167, https://doi.org/10.1073/pnas.0406976102.
[46] B.M. Dufty, L.R. Warner, S.T. Hou, S.X. Jiang, T. Gomez-Isla, K.M. Leenhouts, J.T. Oxford, M.B. Feany, E. Masliah, T.T. Rohn, Calpain-cleavage of α-synuclein: connecting proteolytic processing to disease-linked aggregation, Am. J. Pathol. 170 (2007) 1725–1738, https://doi.org/10.2353/ajpath.2007.061232.
[47] A. Takeda, M. Hashimoto, M. Mallory, M. Sundsumo, L. Hansen, A. Sisk, E. Masliah, Abnormal distribution of the non-a-β component of alzheimers-disease amyloid precursor/α-synuclein in lewy body disease as revealed by proteinase k and formic acid pretreatment, Lab. Investig. 78 (1998) 1169–1177.
[48] V.N. Uversky, J. Li, A.L. Fink, Evidence for a partially folded intermediate in α-Synuclein fibril formation, J. Biol. Chem. 276 (2001) 10737–10744, https://doi.org/10.1074/jbc.M010907200.
[49] M.J. Volles, P.T. Lansbury, Zeroing in on the pathogenic form of α-Synuclein and its mechanism of neurotoxicity in Parkinson's disease, Biochemistry 42 (2003) 7871–7878, https://doi.org/10.1021/bi030086j.
[50] M.G. Spillantini, M.L. Schmidt, V.M.Y. Lee, J.Q. Trojanowski, R. Jakes, M. Goedert, α-Synuclein in Lewy bodies, Nature 388 (1997) 839–840, https://doi.org/10.1038/42166.
[51] M.G. Spillantini, R.A. Crowther, R. Jakes, M. Hasegawa, M. Goedert, Alpha-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with lewy bodies, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 6469–6473.
[52] I.G. McKeith, B.F. Boeve, D.W. DIckson, G. Halliday, J.P. Taylor, D. Weintraub, D. Aarsland, J. Galvin, J. Attems, C.G. Ballard, A. Bayston, T.G. Beach, F. Blanc, N. Bohnen, L. Bonanni, J. Bras, P. Brundin, D. Burn, A. Chen-Plotkin, J.E. Duda, O. El-Agnaf, H. Feldman, T.J. Ferman, D. Ffytche, H. Fujishiro, D. Galasko, J.G. Goldman, S.N. Gomperts, N.R. Graff-Radford, L.S. Honig, A. Iranzo, K. Kantarci, D. Kaufer, W. Kukull, V.M.Y. Lee, J.B. Leverenz, S. Lewis, C. Lippa, A. Lunde, M. Masellis, E. Masliah, P. McLean, B. Mollenhauer, T.J. Montine, E. Moreno, E. Mori, M. Murray, J.T. O'Brien, S. Orimo, R.B. Postuma, S. Ramaswamy, O.A. Ross, D.P. Salmon, A. Singleton, A. Taylor, A. Thomas, P. Tiraboschi, J.B. Toledo, J.Q. Trojanowski, D. Tsuang, Z. Walker, M. Yamada, K. Kosaka, Diagnosis and management of dementia with Lewy bodies, Neurology 89 (2017) 88–100, https://doi.org/10.1212/WNL.0000000000004058.
[53] P.H. Tu, J.E. Galvin, M. Baba, B. Giasson, T. Tomita, S. Leight, S. Nakajo, T. Iwatsubo, J.Q. Trojanowski, V.M.Y. Lee, Glial cytoplasmic inclusions in white matter oligodendrocytes of multiple system atrophy brains contain insoluble α-synuclein, Ann. Neurol. 44 (1998) 415–422, https://doi.org/10.1002/ana.410440324.
[54] H.T. Whittaker, Y. Qui, C. Bettencourt, H. Houlden, Multiple system atrophy: genetic risks and alpha-synuclein mutations, F1000Research 6 (2017), https://doi.org/10.12688/f1000research.12193.1.
[55] W. Poewe, K. Seppi, C.M. Tanner, G.M. Halliday, P. Brundin, J. Volkmann, A.E. Schrag, A.E. Lang, Parkinson disease - only suppl info 1: imaging biomarkers, Nat. Rev. Dis. Prim. 3 (2017) 1–21, https://doi.org/10.1038/nrdp.2017.13.
[56] L. Parnetti, C. Cicognola, P. Eusebi, D. Chiasserini, Value of cerebrospinal fluid alpha-synuclein species as biomarker in Parkinson's diagnosis and prognosis, Biomark. Med 10 (2016) 35–49, https://doi.org/10.2217/bmm.15.107.
[57] L. Farotti, S. Paciotti, A. Tasegian, P. Eusebi, L. Parnetti, Discovery, validation and optimization of cerebrospinal fluid biomarkers for use in Parkinson's disease, Expert. Rev. Mol. Diagn. 17 (2017) 1–10, https://doi.org/10.1080/14737159.2017.1341312.
[58] B. Mollenhauer, R. Batrla, O. El-Agnaf, D.R. Galasko, H.A. Lashuel, K.M. Merchant, L.M. Shaw, D.J. Selkoe, R. Umek, H. Vanderstichele, H. Zetterberg, J. Zhang, C. Caspell-Garcia, C. Coffey, S.J. Hutten, M. Frasier, P. Taylor, R. Umek, D. Selkoe, B. Mollenhauer, H. Zetterberg, B. Du Bowman, H. Vanderstichele, P. Taylor, O. El-Agnaf, J. Zhang, H.A. Lashuel, B. Hyman, P. Juhasz, M. Ahlijanian, A. Jeromin, L. Parkkinen, C. Soto, S. Lee, A. Caricasole, L. Petricca, K. Paumier, M. Latterich, P. Henning Jensen, K. Merchant, J. Hale, R. Batrla, A. Giese, T. Pochapsky, P. Kotzbauer, T. Bartels, C. Scherzer, N. Kruse, E. Stoops, A. Schmid, A user's guide for α-synuclein biomarker studies in biological fluids: Perianalytical considerations, Mov. Disord. 32 (2017) 1117–1130, https://doi.org/10.1002/mds.27090.

[59] 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. (2017), https://doi.org/10.1002/mds.27110.
[60] W. Sako, N. Murakami, Y. Izumi, R. Kaji, Reduced alpha-synuclein in cerebrospinal fluid in synucleinopathies: evidence from a meta-analysis, Mov. Disord. 29 (2014) 1599–1605, https://doi.org/10.1002/mds.26036.
[61] L. Gao, H. Tang, K. Nie, L. Wang, J. Zhao, R. Gan, J. Huang, R. Zhu, S. Feng, Z. Duan, Y. Zhang, L. Wang, Cerebrospinal fluid alpha-synuclein as a biomarker for Parkinson's disease diagnosis: a systematic review and meta-analysis, Int. J. Neurosci. 125 (2015) 645–654.
[62] F.E. Reesink, A.W. Lemstra, K.D. Van Dijk, H.W. Berendse, W.D.J. Van De Berg, M. Klein, M.A. Blankenstein, P. Scheltens, M.M. Verbeek, W.M. Van Der Flier, CSF α-synuclein does not discriminate dementia with Lewy bodies from Alzheimer's disease, J. Alzheimers Dis. 22 (2010) 87–95, https://doi.org/10.3233/JAD-2010-100186.
[63] D. Chiasserini, L. Biscetti, P. Eusebi, N. Salvadori, G. Frattini, S. Simoni, N. De Roeck, N. Tambasco, E. Stoops, H. Vanderstichele, S. Engelborghs, B. Mollenhauer, P. Calabresi, L. Parnetti, Differential role of CSF fatty acid binding protein 3, alpha-synuclein, and Alzheimer's disease core biomarkers in Lewy body disorders and Alzheimer's dementia, Alzheimers Res. Ther. 9 (2017) 52, https://doi.org/10.1186/s13195-017-0276-4.
[64] B. Zhou, M. Wen, W.F. Yu, C.L. Zhang, L. Jiao, The diagnostic and differential diagnosis utility of cerebrospinal fluid α -synuclein levels in Parkinson's disease: a meta-analysis, Parkinsons. Dis. 2015 (2015), https://doi.org/10.1155/2015/567386.
[65] B. Mollenhauer, V. Cullen, I. Kahn, B. Krastins, T.F. Outeiro, I. Pepivani, J. Ng, W. Schulz-Schaeffer, H.A. Kretzschmar, P.J. McLean, C. Trenkwalder, D.A. Sarracino, J.-P. Vonsattel, J.J. Locascio, O.M.A. El-Agnaf, M.G. Schlossmacher, Direct quantification of CSF alpha-synuclein by ELISA and first cross-sectional study in patients with neurodegeneration, Exp. Neurol. 213 (2008) 315–325, https://doi.org/10.1016/j.expneurol.2008.06.004.
[66] S. Hall, Y. Surova, A. Ohrfelt, H. Zetterberg, D. Lindqvist, O. Hansson, A. Öhrfelt, 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.
[67] 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.
[68] D.C. Backstrom, M. Eriksson Domellof, J. Linder, B. Olsson, A. Ohrfelt, 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.
[69] C. Caspell-Garcia, T. Simuni, D. Tosun-Turgut, I.-W. Wu, Y. Zhang, M. Nalls, A. Singleton, L.A. Shaw, J.-H. Kang, J.Q. Trojanowski, A. Siderowf, C. Coffey, S. Lasch, D. Aarsland, D. Burn, L.M. Chahine, A.J. Espay, E.D. Foster, K.A. Hawkins, I. Litvan, I. Richard, D. Weintraub, Parkinson's progression markers initiative (PPMI), multiple modality biomarker prediction of cognitive impairment in prospectively followed de novo Parkinson disease, PLoS One 12 (2017) e0175674, , https://doi.org/10.1371/journal.pone.0175674.
[70] T. Stewart, C. Liu, C. Ginghina, K.C. Cain, P. Auinger, B. Cholerton, M. Shi, J. Zhang, Cerebrospinal fluid α-Synuclein predicts cognitive decline in Parkinson disease progression in the DATATOP cohort, Am. J. Pathol. 184 (2014) 966–975, https://doi.org/10.1016/j.ajpath.2013.12.007.
[71] M.G. Førland, A. Öhrfelt, I. Dalen, O.-B. Tysnes, K. Blennow, H. Zetterberg, K.F. Pedersen, G. Alves, J. Lange, Evolution of cerebrospinal fluid total α-synuclein in Parkinson's disease, Parkinsonism Relat. Disord. 49 (2018) 4–8, https://doi.org/10.1016/j.parkreldis.2018.01.018.
[72] 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.
[73] 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, Alzheimers Res. Ther. 6 (2014), https://doi.org/10.1186/alzrt255.
[74] B. Mollenhauer, H. Esselmann, C. Trenkwalder, W. Schulz-Schaeffer, H. Kretzschmar, M. Otto, J. Wiltfang, M. Bibl, CSF amyloid-β peptides in Neuropathologically diagnosed dementia with Lewy bodies and Alzheimer's disease, J. Alzheimers Dis. 24 (2011) 383–391, https://doi.org/10.3233/JAD-2011-101551.
[75] F. Llorens, M. Schmitz, D. Varges, N. Kruse, N. Gotzmann, K. Gmitterová, B. Mollenhauer, I. Zerr, Cerebrospinal α-synuclein in α-synuclein aggregation disorders: tau/α-synuclein ratio as potential biomarker for dementia with Lewy bodies, J. Neurol. 263 (2016) 2271–2277, https://doi.org/10.1007/s00415-016-8259-0.
[76] 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.
[77] 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) 7, , https://doi.org/10.1186/s13024-016-0072-9.
[78] L. Parnetti, A. Castrioto, D. Chiasserini, E. Persichetti, N. Tambasco, O. El-Agnaf, P. Calabresi, Cerebrospinal fluid biomarkers in Parkinson disease, Nat. Rev. Neurol. 9 (2013) 131–140, https://doi.org/10.1038/nrneurol.2013.10.
[79] M. Delgado-Alvarado, B. Gago, A. Gorostidi, H. Jiménez-Urbieta, R. Dacosta-Aguayo, I. Navalpotro-Gómez, J. Ruiz-Martínez, A. Bergareche, J.F. Martí-Massó, P. Martínez-Lage, A. Izagirre, M.C. Rodríguez-Oroz, Tau/α-synuclein ratio and inflammatory proteins in Parkinson's disease: an exploratory study, Mov. Disord. 32 (2017), https://doi.org/10.1002/mds.27001.
[80] S. Hall, A. Öhrfelt, R. Constantinescu, U. Andreasson, Y. Surova, F. Bostrom, C. Nilsson, W. Håkan, H. Decraemer, K. Någga, 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.
[81] S. Paciotti, G. Bellomo, L. Gatticchi, L. Parnetti, Are we ready for detecting α-synuclein prone to aggregation in patients? The case of "Protein-Misfolding Cyclic Amplification" and "Real-Time Quaking-Induced Conversion" as diagnostic tools, Front. Neurol. 9 (2018), https://doi.org/10.3389/fneur.2018.00415.
[82] G. Fairfoul, L.I. McGuire, S. Pal, J.W. Ironside, J. Neumann, S. Christie, C. Joachim, M. Esiri, S.G. Evetts, M. Rolinski, F. Baig, C. Ruffmann, R. Wade-Martins, M.T.M. Hu, L. Parkkinen, A.J.E. Green, Alpha-synuclein RT-QuIC in the CSF of patients with alpha-synucleinopathies, Ann. Clin. Transl. Neurol. 3 (2016) 812–818, https://doi.org/10.1002/acn3.338.
[83] M. Shahnawaz, T. Tokuda, M. Waragai, N. Mendez, R. Ishii, C. Trenkwalder, B. Mollenhauer, C. Soto, Development of a Biochemical Diagnosis of Parkinson Disease by Detection of α-Synuclein Misfolded Aggregates in Cerebrospinal Fluid, vol. 74, (2017), pp. 163–172, https://doi.org/10.1001/jamaneurol.2016.4547.
[84] B.R. Groveman, C.D. Orrù, A.G. Hughson, L.D. Raymond, G. Zanusso, B. Ghetti, K.J. Campbell, J. Safar, D. Galasko, B. Caughey, Rapid and ultra-sensitive quantitation of disease-associated α-synuclein seeds in brain and cerebrospinal fluid by αSyn RT-QuIC, Acta Neuropathol. Commun. 6 (2018) 7, , https://doi.org/10.1186/s40478-018-0508-2.
[85] W. Peelaerts, L. Bousset, A. Van der Perren, A. Moskalyuk, R. Pulizzi, M. Giugliano, C. Van den Haute, R. Melki, V. Baekelandt, α-Synuclein strains cause distinct synucleinopathies after local and systemic administration, Nature 522 (2015) 340–344, https://doi.org/10.1038/nature14547.
[86] J.L. Guo, D.J. Covell, J.P. Daniels, M. Iba, A. Stieber, B. Zhang, D.M. Riddle, L.K. Kwong, Y. Xu, J.Q. Trojanowski, V.M.Y. Lee, Distinct α-synuclein strains differentially promote tau inclusions in neurons, Cell 154 (2013) 103–117, https://doi.org/10.1016/j.cell.2013.05.057.
[87] C. Peng, R.J. Gathagan, V.M.-Y. Lee, Distinct α-Synuclein strains and implications for heterogeneity among α-Synucleinopathies, Neurobiol. Dis. 109 (2018) 209–218, https://doi.org/10.1016/j.nbd.2017.07.018.
[88] L. Bousset, L. Pieri, G. Ruiz-Arlandis, J. Gath, P.H. Jensen, B. Habenstein, K. Madiona, V. Olieric, A. Böckmann, B.H. Meier, R. Melki, Structural and functional characterization of two alpha-synuclein strains, Nat. Commun. 4 (2013) 2575, , https://doi.org/10.1038/ncomms3575.
[89] M. Vilar, H.-T. Chou, T. Lührs, S.K. Maji, D. Riek-Loher, R. Verel, G. Manning, H. Stahlberg, R. Riek, The fold of alpha-synuclein fibrils, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 8637–8642, https://doi.org/10.1073/pnas.0712179105.
[90] T. Hara, K. Nakamura, M. Matsui, A. Yamamoto, Y. Nakahara, R. Suzuki-Migishima, M. Yokoyama, K. Mishima, I. Saito, H. Okano, N. Mizushima, Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice, Nature 441 (2006) 885–889, https://doi.org/10.1038/nature04724.
[91] M. Komatsu, S. Waguri, T. Chiba, S. Murata, J. Iwata, I. Tanida, T. Ueno, M. Koike, Y. Uchiyama, E. Kominami, K. Tanaka, Loss of autophagy in the central nervous system causes neurodegeneration in mice, Nature 441 (2006) 880–884, https://doi.org/10.1038/nature04723.
[92] R.A. Nixon, The role of autophagy in neurodegenerative disease, Nat. Med. 19 (2013) 983–997, https://doi.org/10.1038/nm.3232.
[93] E. Sidransky, M.A. Nalls, J.O. Aasly, J. Aharon-Peretz, G. Annesi, E.R. Barbosa, A. Bar-Shira, D. Berg, J. Bras, A. Brice, C.-M. Chen, L.N. Clark, C. Condroyer, E.V. De Marco, A. Dürr, M.J. Eblan, S. Fahn, M.J. Farrer, H.-C. Fung, Z. Gan-Or, T. Gasser, R. Gershoni-Baruch, N. Giladi, A. Griffith, T. Gurevich, C. Januario, P. Kropp, A.E. Lang, G.-J. Lee-Chen, S. Lesage, K. Marder, I.F. Mata, A. Mirelman, J. Mitsui, I. Mizuta, G. Nicoletti, C. Oliveira, R. Ottman, A. Orr-Urtreger, L.V. Pereira, A. Quattrone, E. Rogaeva, A. Rolfs, H. Rosenbaum, R. Rozenberg, A. Samii, T. Samaddar, C. Schulte, M. Sharma, A. Singleton, M. Spitz, E.-K. Tan, N. Tayebi, T. Toda, A.R. Troiano, S. Tsuji, M. Wittstock, T.G. Wolfsberg, Y.-R. Wu, C.P. Zabetian, Y. Zhao, S.G. Ziegler, Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease, N. Engl. J. Med. 361 (2009) 1651–1661, https://doi.org/10.1056/NEJMoa0901281.
[94] M.A. Nalls, R. Duran, G. Lopez, M. Kurzawa-Akanbi, I.G. McKeith, P.F. Chinnery, C.M. Morris, J. Theuns, D. Crosiers, P. Cras, S. Engelborghs, P.P. De Deyn, C. Van Broeckhoven, D.M.A. Mann, J. Snowden, S. Pickering-Brown, N. Halliwell, Y. Davidson, L. Gibbons, J. Harris, U.-M. Sheerin, J. Bras, J. Hardy, L. Clark, K. Marder, L.S. Honig, D. Berg, W. Maetzler, K. Brockmann, T. Gasser, F. Novellino, A. Quattrone, G. Annesi, E.V. De Marco, E. Rogaeva, M. Masellis, S.E. Black, J.M. Bilbao, T. Foroud, B. Ghetti, W.C. Nichols, N. Pankratz, G. Halliday, S. Lesage, S. Klebe, A. Durr, C. Duyckaerts, A. Brice, B.I. Giasson, J.Q. Trojanowski, H.I. Hurtig, N. Tayebi, C. Landazabal, M.A. Knight, M. Keller, A.B. Singleton, T.G. Wolfsberg, E. Sidransky, A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies, JAMA Neurol 70 (2013)

727–735, https://doi.org/10.1001/jamaneurol.2013.1925.
[95] H.Q. Rana, M. Balwani, L. Bier, R.N. Alcalay, Age-specific Parkinson disease risk in GBA mutation carriers: information for genetic counseling, Genet. Med. 15 (2013) 146–149, https://doi.org/10.1038/gim.2012.107.
[96] L. Parnetti, D. Chiasserini, E. Persichetti, P. Eusebi, S. Varghese, M.M. Qureshi, A. Dardis, M. Deganuto, C. De Carlo, A. Castrioto, C. Balducci, S. Paciotti, N. Tambasco, B. Bembi, L. Bonanni, M. Onofrj, A. Rossi, T. Beccari, O. El-Agnaf, P. Calabresi, Cerebrospinal fluid lysosomal enzymes and alpha-synuclein in Parkinson's disease, Mov. Disord. 29 (2014) 1019–1027, https://doi.org/10.1002/mds.25772.
[97] C. Balducci, L. Pierguidi, E. Persichetti, L. Parnetti, M. Sbaragli, C. Tassi, A. Orlacchio, P. Calabresi, T. Beccari, A. Rossi, Lysosomal hydrolases in cerebrospinal fluid from subjects with Parkinson's disease, Mov. Disord. 22 (2007) 1481–1484, https://doi.org/10.1002/mds.21399.
[98] L. Parnetti, S. Paciotti, P. Eusebi, A. Dardis, S. Zampieri, D. Chiasserini, A. Tasegian, N. Tambasco, B. Bembi, P. Calabresi, T. Beccari, Cerebrospinal fluid β-glucocerebrosidase activity is reduced in parkinson's disease patients, Mov. Disord. 32 (2017) 1423–1431, https://doi.org/10.1002/mds.27136.
[99] L. Parnetti, C. Balducci, L. Pierguidi, C. De Carlo, M. Peducci, C. D'Amore, C. Padiglioni, S. Mastrocola, E. Persichetti, S. Paciotti, G. Bellomo, N. Tambasco, A. Rossi, T. Beccari, P. Calabresi, Cerebrospinal fluid β-glucocerebrosidase activity is reduced in dementia with Lewy bodies, Neurobiol. Dis. 34 (2009) 484–486, https://doi.org/10.1016/j.nbd.2009.03.002.
[100] V. Pisani, A. Stefani, M. Pierantozzi, S. Natoli, P. Stanzione, D. Franciotta, A. Pisani, Increased blood-cerebrospinal fluid transfer of albumin in advanced Parkinson's disease, J. Neuroinflammation 9 (2012) 188, https://doi.org/10.1186/1742-2094-9-188.
[101] S. Janelidze, D. Lindqvist, V. Francardo, S. Hall, H. Zetterberg, K. Blennow, C.H. Adler, T.G. Beach, G.E. Serrano, D. Van Westen, E. Londos, M.A. Cenci, O. Hansson, Increased CSF biomarkers of angiogenesis in Parkinson disease, Neurology 85 (2015) 1834–1842, https://doi.org/10.1212/WNL.0000000000002151.
[102] F. Llorens, M. Schmitz, S.F. Gloeckner, L. Kaerst, P. Hermann, C. Schmidt, D. Varges, I. Zerr, Increased albumin CSF/serum ratio in dementia with Lewy bodies, J. Neurol. Sci. 358 (2015) 398–403, https://doi.org/10.1016/j.jns.2015.10.011.
[103] P.S. Sastry, Lipids of nervous tissue: composition and metabolism, Prog. Lipid Res. (1985), https://doi.org/10.1016/0163-7827(85)90011-6.
[104] G.S. Hotamisligil, D.A. Bernlohr, Metabolic functions of FABPs - mechanisms and therapeutic implications, Nat. Rev. Endocrinol. 11 (2015) 592–605, https://doi.org/10.1038/nrendo.2015.122.
[105] F.N. Sepe, D. Chiasserini, L. Parnetti, Role of FABP3 as biomarker in Alzheimer's disease and synucleinopathies, Future Neurol. 13 (2018) 199–207, https://doi.org/10.2217/fnl-2018-0003.
[106] D. Chiasserini, L. Parnetti, U. Andreasson, H. Zetterberg, D. Giannandrea, P. Calabresi, K. Blennow, CSF levels of heart fatty acid binding protein are altered during early phases of Alzheimer's disease, J. Alzheimers Dis. 22 (2010) 1281–1288, https://doi.org/10.3233/JAD-2010-101293.
[107] H. Zetterberg, Applying fluid biomarkers to Alzheimer's disease, Am. J. Physiol. Cell Physiol. 313 (2017) C3–C10, https://doi.org/10.1152/ajpcell.00007.2017.
[108] K.H. Braunewell, The visinin-like proteins VILIP-1 and VILIP-3 in Alzheimer's disease—old wine in new bottles, Front. Mol. Neurosci. 5 (2012), https://doi.org/10.3389/fnmol.2012.00020.
[109] M.I. Kester, C.E. Teunissen, C. Sutphen, E.M. Herries, J.H. Ladenson, C. Xiong, P. Scheltens, W.M. Van Der Flier, J.C. Morris, D.M. Holtzman, A.M. Fagan, Cerebrospinal fluid VILIP-1 and YKL-40, candidate biomarkers to diagnose, predict and monitor Alzheimer's disease in a memory clinic cohort, Alzheimers Res. Ther. (2015), https://doi.org/10.1186/s13195-015-0142-1.
[110] J.M. Lee, K. Blennow, N. Andreasen, O. Laterza, V. Modur, J. Olander, F. Gao, M. Ohlendorf, J.H. Ladenson, The brain injury biomarker VLP-1 is increased in the cerebrospinal fluid of Alzheimer disease patients, Clin. Chem. (2008), https://doi.org/10.1373/clinchem.2008.104497.
[111] D. Stejskal, L. Sporova, M. Svestak, M. Karpisek, Determination of serum visinin like protein-1 and its potential for the diagnosis of brain injury due to the stroke - a pilot study, Biomed. Pap. (2011), https://doi.org/10.5507/bp.2011.049.
[112] X. Hu, Y. Yang, D. Gong, A meta-analysis of cerebrospinal fluid visinin-like protein-1 in Alzheimer's disease patients relative to healthy controls and mild cognitive impairment patients, Neurosciences 22 (2017) 94–101, https://doi.org/10.17712/nsj.2017.2.20160557.
[113] M. Babić Leko, F. Borovečki, N. Dejanović, P.R. Hof, G. Simić, Predictive value of cerebrospinal fluid Visinin-like Protein-1 levels for Alzheimer's disease early detection and differential diagnosis in patients with mild cognitive impairment, J. Alzheimers Dis. 50 (2016), https://doi.org/10.3233/JAD-150705.
[114] K. Fuxe, A.B. Dahlström, G. Jonsson, D. Marcellino, M. Guescini, M. Dam, P. Manger, L. Agnati, The discovery of central monoamine neurons gave volume transmission to the wired brain, Prog. Neurobiol. 90 (2010) 82–100, https://doi.org/10.1016/j.pneurobio.2009.10.012.
[115] G. Aston-Jones, B. Waterhouse, Locus coeruleus: from global projection system to adaptive regulation of behavior, Brain Res. 1645 (2016) 75–78, https://doi.org/10.1016/j.brainres.2016.03.001.
[116] D. Aarsland, S. Påhlhagen, C.G. Ballard, U. Ehrt, P. Svenningsson, Depression in Parkinson disease - epidemiology, mechanisms and management, Nat. Rev. Neurol. 8 (2012) 35–47, https://doi.org/10.1038/nrneurol.2011.189.
[117] Y. Vermeiren, D. Van Dam, T. Aerts, S. Engelborghs, J.J. Martin, P.P. De Deyn, The monoaminergic footprint of depression and psychosis in dementia with Lewy bodies compared to Alzheimer's disease, Alzheimers Res. Ther. 7 (2015), https://doi.org/10.1186/s13195-014-0090-1.
[118] P.J. Langlais, L. Thal, L. Hansen, D. Galasko, M. Alford, E. Masliah, Neurotransmitters in basal ganglia and cortex of Alzheimer's disease with and without Lewy bodies, Neurology 43 (10) (1993) 1927–1934 (doi:DLB-Converted #37).
[119] S. van der Zee, Y. Vermeiren, T. Aerts, D. van Dam, M.J. Gerritsen, J.M. Spikman, T. van Laar, P.P. de Deyn, Monoaminergic biomarkers of cognitive decline in Parkinson's disease and Lewy body dementia, Mov. Disord. 31 (2016) S468.
[120] J. Janssens, Y. Vermeiren, E. Fransen, T. Aerts, D. Van Dam, S. Engelborghs, P.P. De Deyn, Cerebrospinal fluid and serum MHPG improve Alzheimer's disease versus dementia with Lewy bodies differential diagnosis, Alzheimer's Dement. Diagnosis, Assess. Dis. Monit. 10 (2018) 172–181, https://doi.org/10.1016/j.dadm.2018.01.002.
[121] M.B. Aerts, R.A.J. Esselink, J.A.H.R. Claassen, W.F. Abdo, B.R. Bloem, M.M. Verbeek, CSF Tau, Aβ42, and MHPG differentiate dementia with Lewy bodies from Alzheimer's disease, J. Alzheimers Dis. 27 (2011) 377–384, https://doi.org/10.3233/JAD-2011-110482.