BLOOD AND CEREBROSPINAL FLUID BIOMARKERS OF COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease, characterized by dopaminergic neuronal loss in substantia nigra and α-synuclein accumulation in intraneuronal aggregates. Apart from the cardinal motor symptoms, non-motor features are also evident; among them, cognitive impairment is a consistent finding in PD patients, who are susceptible to an increased dementia risk. Progressing cognitive decline includes the stages of subjective cognitive decline, mild cognitive impairment (MCI) and dementia. Various mechanisms contribute to each of these stages, whereas responsible neuropathological correlates have been investigated in clinicopathological correlation studies. Longitudinal studies focus on the prognostic value of different molecules in assessments of cognitive decline over time. The composition of the cerebrospinal fluid (CSF) reflects brain metabolism and neuronal condition; hence, CSF proteins may be promising biomarkers of cognitive dysfunction mechanisms in PD. Plasma and serum studies have also revealed candidate biomarkers for assessing cognition in PD. Since MCI conversion to dementia is variable, biomarkers that enhance early identification of cognitive dysfunction factors and prediction of dementia risk are necessary. This review summarizes recent studies of promising blood and CSF biomarkers of PD-related cognitive impairment. Several correlates of neuronal damage have been shown indicative of poor cognitive performance and predicted cognitive deterioration, including amyloid-β and neurofilament light chain. Inflammatory factors, lysosomal dysfunction, oxidative stress and genetic variants could be also useful in assessing cognitive decline in PD. Future research is needed for the validation of the candidate biomarkers, recognizing the potential benefit of robust biomarkers in clinical practice and their implementation in clinical trials.

Key-words: Parkinson's disease; cognitive impairment; biomarkers; cerebrospinal fluid; blood

ΒΙΟΔΕΙΚΤΕΣ ΝΟΗΤΙΚΗΣ ΕΚΠΤΩΣΗΣ ΣΤΟ ΕΓΚΕΦΑΛΟΝΩΤΙΑΙΟ ΥΓΡΟ ΚΑΙ ΤΟ ΑΙΜΑ ΣΤΗ ΝΟΣΟ ΤΟΥ ΠΑΡΚΙΝΣΟΝ

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Περίληψη

Η νόσος του Πάρκινσον (ΝΠ) αποτελεί τη δεύτερη συχνότερη νευροεκφυλιστική νόσο, η οποία χαρακτηρίζεται από την απώλεια ντοπαμινεργικών νευρώνων στην μέλαινα ουσία και την συσσώρευση α-συνουκλεΐνης σε ενδοκυττάρια νευρωνικά έγκλειστα. Πέραν των κινητικών συμπτωμάτων της νόσου, συνυπάρχουν επίσης μη-κινητικά συμπτώματα. Εξ αυτών, η νοητική έκπτωση είναι συνήθης σε ασθενείς με Πάρκινσον, οι οποίοι βρίσκονται σε αυξημένο κίνδυνο εμφάνισης άνοιας. Η προοδευτικά επιδεινούμενη νοητική έκπτωση περιλαμβάνει την υποκειμενική νοητική έκπτωση, την ήπια νοητική έκπτωση (MCI) και την άνοια. Νευροπαθολογικά υποστρώματα των υποκείμενων παθοφυσιολογικών μηχανισμών έχουν ερευνηθεί σε μελέτες κλινικοπαθολογικής συσχέτισης. Μελέτες παρακολούθησης επικεντρώνονται στην προγνωστική αξία δεικτών κατά την αξιολόγηση της προόδου της νοητικής έκπτωσης στον χρόνο. Ο μεταβολισμός του εγκεφάλου κι η υγεία του νευρώνα εκπροσωπούνται στο εγκεφαλονωτιαίο υγρό (ΕΝΥ), μέσω πρωτεϊνών οι οποίες συνεισφέρουν ως πιθανοί βιοδείκτες των μηχανισμών νοητικής δυσλειτουργίας στην ΝΠ. Επιπλέον, βιοδείκτες νοητικής έκπτωσης δύναται να ανευρεθούν στον ορό και το πλάσμα αίματος. Δεδομένης της ασταθούς μετάπτωσης από την MCI σε άνοια, οι βιοδείκτες είναι αναγκαίοι για την πρώιμη ανίχνευση γνωστικών ελλειμμάτων και την πρόβλεψη του κινδύνου άνοιας. Η παρούσα ανασκόπηση συνοψίζει πρόσφατες μελέτες υπό-διερεύνηση βιοδεικτών, στο αίμα και το ΕΝΥ, της νοητικής έκπτωσης στην ΝΠ. Διάφοροι δείκτες νευρωνικής βλάβης έχουν συσχετιστεί με πτωχή νοητική λειτουργία και προβλέπουν γνωστική επιδείνωση, όπως το β-αμυλοειδές και τα νευροϊνίδια. Φλεγμονώδεις παράγοντες, το οξειδωτικό στρες, η λυσοσωμιακή δυσλειτουργία και γενετι-

κές παραλλαγές συνεισφέρουν επίσης στην νοητική έκπτωση. Μελλοντικές μελέτες είναι αναγκαίες ώστε να εδραιωθούν οι υποψήφιοι βιοδείκτες, δεδομένου του οφέλους που θα συνεισφέρουν στην κλινική πράξη και τον σχεδιασμό κλινικών μελετών.

Λέξεις-κλειδιά:νόσος του Πάρκινσον, νοητική έκπτωση, βιοδείκτες, εγκεφαλονωτιαίο υγρό, αίμα

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, which is characterized by the loss of dopaminergic neurons in the substantia nigra (SN) and the subsequent pathological accumulation of a-synuclein in intraneural cellular inclusion [1]. These pathological protein aggregates are known as Lewy bodies. Apart from proteinopathy, several mechanisms contribute to the pathogenesis of PD,including Alzheimer's disease (AD)- related pathology, neuroinflammation, oxidative stress and neurotransmitter deficiency, as well as genetic variations [2]. The cardinal motor features of PD are bradykinesia, tremor and rigidity, which are primarily associated with striatal dopaminergic degeneration in SN. Apart from these substantial entities, non-motor symptoms of PD are equally involved in the disease related burden and disability. Cognitive impairment is a highly prevalent clinical feature in PD, affecting even newly diagnosed patients with PD [1].

PD individuals are considered to be at a higher risk, up to 6 times, of developing dementia as compared to similar aged non-PD individuals [2]. The spectrum of cognitive dysfunction in PD ranges accordingly from subjective cognitive decline (SCD) to mild cognitive impairment (MCI) and finally to dementia. Although SCD refers to signs of memory deficits that are self-reported and for which patients complain, conversion to MCI requires a diagnostic validation process. Recently, PD-MCI diagnostic criteria were established, defining MCI as SCD reported by patients, caregivers or physicians which is evident by deficits in neuropsychological evaluation, but does not interfere with significant functional independence [3]. Despite the fact that MCI is considered a transitional stage between normal cognition and dementia, the MCI course is variable and time interval to dementia is not definite, since not all patients become demented. Around 60% of PD-MCI individuals have been reported to develop dementia during a 5-year follow-up, reflecting the natural history of cognitive decline in PD [4]. Conversion from MCI to dementia in PD (PDD) is in the majority of cases an inevitable clinical event, determined by certain diagnostic criteria [5] which substantiate cognitive decline in more than one cognitive domain, which should be significant enough in order to negatively influence daily life and lasting for at least 6 months [2].

Neuropsychological assessment is required in order to diagnose cognitive impairment in PD. Both instruments of global cognition evaluation and more detailed neuropsychological tools are also used in clinical practice in order to monitor cognitive dysfunction and to determine the affected domains. Commonly used cognitive screening in PD includes the Montreal Cognitive Assessment (MoCA) [6], Mini Mental State Examination (MMSE), Mattis Dementia Rating Scale Second Edition (MDRS-2), Parkinson's Disease- Cognitive Rating Scale (PD-CRS)[7] and Scales for Outcomes in Parkinson's Disease- Cognition (SCOPA-COG)[8]. More targeted neuropsychological tools are implemented in the assessment of the five core cognitive domains: attention and working memory, executive, language, memory and visuospatial function [3].

Identification of cognitive decline in early stages is crucial in order to predict future disease progression and to design therapeutic interventions, aiming to prevent rapid cognitive decline or even to stabilize the cognitive status over a period. For this purpose, the interest in identifying biomarkers of cognitive impairment in PD has been increased in the last decade [9, 10]. Valuable biomarkers, i.e. objective and quantifiable parameters, of cognitive function in PD should either associate with pathological processes of the disease and discriminate between cognitive impaired (PD-CI) and non- cognitive impaired (PD-NCI) PD patients, or predict cognitive decline and the conversion to dementia.

Methods

Herein, we investigated the current literature to review candidate molecular biomarkers of cognitive dysfunction in PD. Our PubMed search was based on articles published from January 2010 to September 2023, in English language. Specific terms were used in order to form accurate searching algorithms, including: ("Parkinson's disease" OR PD) AND biomarker* AND ("cerebrospinal fluid" OR CSF OR serum OR blood OR plasma) AND ("cognitive impairment" OR "cognitive decline").

α-synuclein

The aggregates of α-synuclein are definite hallmarks of PDD neuropathology via their deposition in brainstem and olfactory domains, resulting in synaptic dysfunction due to loss of monoaminergic and

cholinergic neurons. The infiltration of limbic system (parahippocampal) and neocortex, involving frontal and temporal structures, with α-synuclein aggregates is associated with the development of cognitive impairment. Furthermore, in PD, α-synuclein pathology interacts with DNA repair processes, affecting neuronal DNA. Involvement of α-synuclein in neuroinflammation has been also suggested, with recent evidence supporting the role of α-synuclein in the activation of type 1 interferon, promoting neurodegeneration [11]. α-Synuclein aggregation is a complicated procedure, involving multiple protein-protein interactions, of which phosphorylation seems to promote LB formation and neuronal degeneration [12]. Apart from idiopathic PD, genetic variations of the SNCA gene, the encoding gene of α-synuclein, are directly associated with pathological α-synuclein isoforms and the increased dementia risk. Other PD-related genes, including LRRK2 and GBA, have been related to α-synucleinpathology as well, promoting aggregation via phosphorylation (LRRK2) and stabilizing soluble oligomeric intermediates (GBA).

CSF levels of α-synuclein have been studied as biomarkers of cognitive decline in PD, with evidence by relevant studies being inconsistent. In CSF studies, levels of α-synuclein have been found comparable or lower in PD subjects than in healthy controls [13-15]. Early studies have shown that increased CSF concentrations of α-synuclein predicted the progression of cognitive decline over time, as shown, among other studies, by the DATATOP cohort, where PD subjects with higher CSF α-synuclein had a faster cognitive decline [16-18]. Lower CSF α-synuclein was significantly associated with reduced performance on executive/attention domains and decreased composite cognitive score in the study by Skogseth et el. [15], as well as with deficits in phonetic fluency [19]. Higher baseline CSF α-synuclein concentrations were also related to worse performance in longitudinal assessments of affective and executive functioning domains [20]. In contrary, it was also showed that concentrations of α-synuclein were lower in PD-CI as compared to PD-NCI subjects [21]. Several studies revealed none significant relationship between CSF α-synuclein levels and cognitive decline, neither in single baseline measurements nor in longitudinal assessments, in PDD and PD-MCI subjects [13, 14, 18, 22-25]. Apart from total α-synuclein, posttranslational forms (i.e. ubiquinated, phosphorylated, nitrated or oligomeric forms) could indicate cognitive decline. Oligomeric α-synuclein levels in CSF have been found to be elevated in PDD subjects as compared to controls, yet no association was detected with cognitive deficits [19, 26]. Higher CSF phosphorylated α-synuclein and the ratio of phosphorylated-α-synuclein/total-α-synuclein were correlated with better executive functioning [27].

Elevated plasma levels of α-synuclein have been found in PD subjects as compared to healthy controls in several studies [28-31], while PD-CI subjects had also a higher plasma α-synuclein as compared to PD-NCI [29-31]. Performance in frontal lobe-mediated tasks was linked to plasma α-synuclein levels [31]. Higher plasma α-synuclein was associated with an increased risk of PD-MCI [30]. Plasma α-synuclein has been either positively or negatively correlated to MMSE score [29, 32], whereas lower plasma α-synuclein was indicative of cognitive decline in MoCA, FAB and RAVLT assessments [33]. Blommer et al. detected a lower neuronal extracellular vesicle α-synuclein in PD-CI as compared to PD-NCI subjects [34].

β-Amyloid

Apart from α-synuclein aggregates which constitute the hallmark of PD pathogenesis, it is well established that AD-related pathology contributes to cognitive impairment in PD, via extracellular β-amyloid (Aβ) and intracellular tau accumulation and deposition [2]. The overlap between the two neurodegenerative diseases involves Aβ plaques and tau tangles and was originally identified in post-mortem histological studies, which detected Aβ deposition in cortical and subcortical regions in about 50% of PDD subjects. Almost 1/3 of total PDD subjects had severe tau pathology in hippocampal and neocortical domains [35]. AD pathology is suggested to accelerate the progressing cognitive decline in PD via amyloid angiopathy and neuroinflammation, reflecting deficits in multiple cognitive domains [2, 35]. Given the established role of Aβ as biomarker in AD, several studies investigated the diagnostic and predictive value of this molecule in assessing cognition impairment in PD, both in cross-sectional and longitudinal studies. Several research groups investigating PDD individuals found that CSF $A\beta_{42}$ levels are commonly decreased in demented patients as compared to non-demented patients and/or healthy controls [19, 21, 36, 37]. A meta-analysis by Hu et al. suggested that CSF $A\beta_{42}$ was primarily associated with cases of PD-CI rather than PD-MCI individuals, since evidence from different studies also varied regarding comparisons of Aβ42 levels between mild cognitive impairment and normal cognition [38].

Studies have shown the association between CSF $A\beta_{42}$ and deficits both in global cognition and individual cognitive domains. Deficits in both MoCA and MMSE scores have been associated with low CSF $A\beta_{42}$ levels in PD [39, 40]. Decreased CSF $A\beta_{42}$ was related to deficits in attention [27, 41, 42], working memory [41], phonemic fluency [43], conceptualization [42], initiation/ preservation [42], memory [14, 42] and response inhibition [14]. Furthermore, Zarifkar et al. found significant correlations between low CSF $A\beta_{42}/A\beta_{40}$ ratio and impairment in attention/ executive function-

ing and language [44]. Higher prevalence of positive amyloidosis profile (low $A\beta_{42}/A\beta_{40}$) in CSF was also reported in PDD as compared to PD-MCI and healthy individuals [45]. $A\beta_{42}$/neurogranin ratio was described as a valuable marker to discriminate between PD-CI and PD-NCI patients, reflecting processes of synaptic dysfunction [46]. Evidence from studies investigating plasma $A\beta_{42}$ levels did not provide a definite association to impaired cognitive performance [30]. However, in the recent study by Lin et al., higher baseline $A\beta_{40}$ predicted a faster cognitive decline [47]. Plasma $A\beta_{40}$ has been associated with impaired cognition; yet, a disagreement between studies should be noted since plasma $A\beta_{40}$ concentrations have been described both increased and decreased in PD [48-50]. A potential advance in Aβ investigations as biomarker in PD was suggested by the findings in the novel study by Wang et al., where $A\beta_{42}$-containing platelet-derived extracellular vesicles (EV) were higher in PDD, as detected using a nano-scale flow cytometry assay [51]. Plasma EV $A\beta_{42}$ was previously shown increased in PD-CI as compared to PD-NCI patients [52].

The value of CSF $A\beta_{42}$ in predicting cognitive dysfunction in PD individuals has been the objective of many studies in the last decade. Overall, $A\beta_{42}$ should be considered an independent prognostic factor of cognitive decline in PD, since evidence from various studies, using different outcome measures and time-frames of the longitudinal assessments, showed that low CSF $A\beta_{42}$ in baseline measurements predicts cognitive impairment and progression to PDD, as well as time to dementia [22, 23, 25, 53-56]. In particular, findings by the Parkinson's Progression Markers Initiative (PPMI) cohort showed gradually decreased CSF $A\beta_{42}$ concentrations during disease progression and association between lower baseline CSF $A\beta_{42}$ and cognitive decline in a 3-year follow-up [53]. Baseline measures of CSF $A\beta_{42}$ were also found to predict memory deficits [22].

Total tau (t-tau) and Phosphorylated 181 tau (p-tau)

In contrast with the relatively definite role of Aβ in the development of cognitive dysfunction and dementia in PD, the contribution of tau in this process is yet to be clarified. Contradictory findings among individual studies demonstrate either increased or decreased [21, 37] levels of CSF t-tau and p-tau in cognitive impaired PD individuals. Notably, a meta-analysis including 590 PD-CI and 1182 PD-NCI patients detected elevated CSF t-tau and p-tau in presence of dementia [38]. Plasma t-tau has been related to cognitive dysfunction [49], including deficits in attention and executive functioning [15, 57] and visuospatial function [15]. Higher CSF p-tau related to worse language functioning in the study by Oosterveld et al. [27], whereas also predicted longitudinal impairments in memory and executive functioning [58]. Increased plasma p-tau in baseline measurements has been shown predictive of faster cognitive decline over time [47], while CSF p-tau increase during disease progression also related to faster cognitive decline [18]. However, other studies failed to identify significant relationships between t-tau, p-tau [55] and impaired cognition in the PD examined population [39, 50, 59]. A recent study revealed significant association of plasma EV tau with cognitive function, using the technological advances in immunoassay field [52].

The combination of AD-pathology markers, in terms of tau/Aβ ratios, seems to generate promising biomarkers of cognitive dysfunction in PD, as revealed by the findings of different studies. High baseline CSF p-tau/$A\beta_{42}$ was associated with faster cognitive decline [60] and subsequent memory and executive function deficits [58], whereas t-tau/$A\beta_{42}$ related to progression to dementia [61]. Plasma tau/$A\beta_{42}$ ratio has been correlated to posterior cortical-mediated tasks [31].

Neurofilament light chain (NfL)

Neurodegeneration and axonal damage result in the release of various subunits of neurofilaments in the interstitial space of CNS. NfL is a cytoskeletal protein, expressed in both central and peripheral neurons, whose injury and degeneration leads to increased CSF and blood concentrations of NfL [62].

Recently, advances were described in the investigation, both in CSF and plasma, of NfL as a biomarker of cognitive impairment in PD, utilizing the development of ultrasensitive techniques to measure these molecules. In the study by Bäckström et al., high CSF NfL in baseline measurements predicted progression to PDD in a 1-year follow-up assessment [23], a finding also observed in later longitudinal studies, which also associated faster cognitive decline to higher baseline CSF NfL [24, 63, 64]. Increased CSF NfL concentrations have been related to worse cognitive performance, in terms of worse MoCA score, as well as deficits in memory, attentional and executive functioning [13, 27, 65]. The value of plasma and serum NfL as a biomarker of cognitive decline has been also shown in recent studies, providing similar findings to that of CSF studies. High plasma NfL levels were associated with thinner temporal and insular cortical thickness, reflecting also posterior cortical neurodegeneration [28, 66]. Higher serum and plasma NfL was associated with worse cognitive performance, i.e. decreased MoCA and multiple cognitive domain scores, and was related to an increased risk of progression to PDD [28, 67-72]. Longitudinal studies of PD subjects showed that serum/plasma NfL increases over time during the disease progression and higher baseline NfL levels predict the cognitive decline in follow-up evaluations [66, 69, 71-73]. Serum/plasma NfL has been

associated not only to impaired global cognition but also to deficits in episodic memory, visuospatial functioning, executive functioning, processing speed, attention and language/verbal fluency [70, 72].

Neuroinflammation

Inflammatory markers

It has been hypothesized that inflammation contributes in the pathological processes of PD progression. Both central-nervous and peripheral, innate and adaptive immune system activation is considered to influence PD pathophysiology, promoted by activated microglia and α-synuclein-induced cytokine production [74]. Based on this hypothesis recent studies investigated the role inflammatory markers as biomarkers of impaired cognition in PD. Higher serum IL-6 levels were reported in PD subjects with cognitive deficits as compared to non-cognitive impaired patients, while significant negative correlations were shown between serum and CSF IL-6, MoCA score and cognitive speed [75-77]. Furthermore, IL-8 and IL-18were also associated with impaired cognitive performance [78-80]. Tumor necrosis factor-a (TNF-a) has been shown as a potential biomarker of cognitive impairment, since higher serum TNF-a related to worse MoCA scores and higher CSF TNF-a in baseline measurements could predict a faster cognitive decline [79, 80]. In investigations of various inflammatory mediators, lower MoCA scores were associated with higher CSF levels of ICAM-1, MCP-1, MIP-1 beta, FABP, SCF and higher serum levels of CA-125, while higher SAA and C-reactive-protein (CRP) were related to worse performance on global cognition, cognitive speed and attention assessments [76, 79, 80]. Interestingly, in the study by Shen et al. a predictive model of measuring three plasma proteins (melanoma inhibitory activity protein, CRP and albumin) identified accurately PD individuals of high risk to develop cognitive impairment [81]. Fibrinogen was also found upregulated in PD-CI subjects and correlated negatively to Wisconsin card sorting score [82].

Other proteins associated with cognitive impairment in PD

Glucoprotein Chitinase-3-like protein 1, also known as YKL-40, as marker of glial activation and inflammation expressed in microglia and astrocytes, was demonstrated to increase in CSF of PD patients in 2-year longitudinal measurements, whereas this increase was associated with a faster cognitive decline [13, 18]. Another microglial activation marker, the soluble fragment of triggering receptor expressed on myeloid cells 2 (sTREM2), could contribute as biomarker in the prediction of cognitive decline in PD, since higher baseline CSF sTREM2 predicted greater future impairment in global cognition [13, 24, 83]. Elevated concentrations of CSF sTREM2 were measured in subgroups of PD patients with a positive CSF tau profile, but not with Aβ [84]. Also derived from astrocytes, glial fibrillary acidic protein (GFAP) was recently investigated regarding its role in cognitive deterioration to dementia. High CSF GFAP at baseline predicted cognitive decline and dementia during longitudinal evaluations [13, 85]. Similarly, elevated plasma GFAP was associated with worse cognitive scores [86], independently contributed to PDD [67] and predicted PD-MCI to PDD conversion [87].

The inflammation-derived oxidative stress is postulated to play a significant role in PD pathogenesis and neurodegeneration, as well as to the potential development of cognitive impairment in PD, since studies also showed associations of worse cognitive performance with high CSF levels of hydroxyl radical (•OH) and low serum nitric oxide levels [75, 88]. As a consequence of cellular oxidative stress in PD, the activated phospholipases cause the lysis of cell membranes and the subsequent release of phospholipids (PL). Increased plasma PL were strongly associated with impaired cognitive performance [89]. Furthermore, abnormal lipid perioxidation may affect cognition in PD. Elevated serum high-density lipoprotein (HDL) levels were associated with worse cognitive performance in ACE-R and SCOPA-COG assessments in females PD patients [90]. Another study described higher levels of total cholesterol, triglyceride and apolipoprotein A1 as independent predictors of mild cognitive impairment in PD [91]. Moreover, potential predictive biomarkers, for which underlying mechanisms to develop dementia in PD are unclear, include low estimated glomerular filtration rate (eGFR) [92] and low serum uric acid [10, 93]. Higher serum homocysteine concentration at baseline also predicted declining MoCA scores in 54-month follow up [94]. Decreased levels of vitamin D were associated with impaired cognition in PD, being valuable in predicting development of mild cognitive impairment over a 48-month period [95, 96].

In the study by Martin-Ruiz et al. investigating senescence and inflammatory markers, higher p16 expression predicted cognitive decline in a 36-month follow-up, as well as shorter telomeres related to dementia over the same period [77]. Various other proteins have been recently associated with cognitive dysfunction in PD: increased acidic isoforms of CSF serpinA1, an acute phase protein, indicated a higher PDD risk [97]; plasma exosomal prion protein concentration was found elevated in PD-CI as compared to PD-NCI and healthy individuals, whereas a significant correlation to the MoCA score was detected [98].

Growth factors

Brain-derived neurotrophic factor (BDNF) is involved in the regulation of dopaminergic neuron

survival and preservation of synaptic plasticity, triggering researchers to explore its role in PD. BDNF plasma levels were positively correlated to cognitive performance assessed by MoCA/MMSE tests [99, 100], as well as in attention, executive, working memory and self-monitoring/inhibition domains [101]. Low concentration of plasma epidermal growth factor (EGF) has been linked to poor performance in cognitive tests, including domains of semantic fluency, verbal memory, attention/executive function and visuospatial abilities, while low baseline plasma EGF also predicted progression to cognitive impairment and dementia [102-104]. Furthermore, decreased plasma levels of glial cell line-derived neutrophic factor (GDNF), a protective neurotrophic factor for dopaminergic neurons, discriminated between PD-CI and PD-NCI patients [105] and could potentially used as biomarker of executive function in PD, including deficits in inhibitory control, cognitive flexibility, and attention performances [106]. Insulin-like growth factor 1 (IGF-1) was associated with poor performance on global cognition and executive tasks [107, 108], with low baseline IGF-1 showing also prognostic value for faster cognitive decline, including attention/executive and verbal memory performance [108].

Genetics

Genetic variations are involved in PD pathogenesis and the determination of the underlying genetic basis in PD is important in order to predict cognitive trajectories. Although Parkin gene- and LRRK2-related PD cases are considered to be associated with a lower risk of cognitive dysfunction, the opposite seems to apply to genetic polymorphisms that affect the encoding of α-synuclein (SNCA gene) and β-glucocerebrosidase (GBA gene) [9]. Apart from gene mutations, transcriptional and post-transcriptional products in plasma and CSF could provide novel insights in search of cognitive biomarkers in PD.

The ε4 allele of APOE, the encoding gene of apolipoprotein E, was associated with the incidence and progression of cognitive dysfunction in PD [10, 109]. Recently, in a genome-wide survival meta-analysis of 3923 PD individuals, APOE ε4 was characterized as a major risk factor of dementia development in PD, whereas a novel locus within APOE and LRP1B gene was also predictive of dementia in PD [110]. E4 allelle was associated with deficits of memory, attention/executive function and language, restricted to learning and semantic verbal fluency impairment in the non-demented subgroup [111], while APOE e4 was related to executive dysfunction in PDMCI patients [112]. A faster deterioration in visuospatial function was also detected for ε4+ PD individuals [22]. The APOE ε4 allele is considered to influence Aβ deposition and other AD-related changes, as suggested by evidence of prognostic correlations between higher baseline Aβ, p-tau and faster cognitive decline in ε4+ carriers [47].

Involved in the degradation of dopamine, genetic variations of the catechol O-methyltransferase (COMT) gene have been linked to cognitive function in PD [113]. Specifically, COMT Val/Val polymorphisms increase dopamine catabolism and predicted cognitive impairment in longitudinal assessments of de novo PD individuals [54], as well as a faster decline in executive function, verbal learning and memory [114]. Polymorphisms in the tau-related MAPT gene were also indicative of cognitive impairment in PD, with the H1/H1 being associated with an increased risk of dementia development [109]. SNCA gene is related to autosomal dominant PD, often characterized by prominent cognitive dysfunction [9]. In a recent study, non carrier status of SNCA rs6826785 single nucleotide polymorphism was identified as an increased risk parameter for mild cognitive impairment in PD [115].

Reduced α-synuclein degradation and pathological accumulation in the process of PD could be promoted by dysfunction of the lysosomal-autophagy system. This pathophysiological pathway is linked to mutations in the encoding gene of β-glucocerebrosidase, the GBA gene, whose pathological variants are regarded as genetic risk factors for cognitive impairment and dementia in PD [110, 116, 117], associated with deficits in working memory, visuospatial and executive functions [118]. Lysosomal dysfunction in PD was further supported by the findings of Parnetti et al., who reported that reduced activity of CSF β-glucocerebrosidase in PD independently of GBA carrier status, whereas dysfunction of CSF β-glucocerebrosidase and β-hexosaminidase associated with worse cognitive performance, supporting the potential of lysosomal enzymes as biomarkers of cognitive decline in PD [119]. Interestingly, a higher CSF glucocerebrosidase/ sphingomyelin ratio was able to predict faster cognitive decline in idiopathic PD individuals in longitudinal MoCA assessments [120].

The exponential research interest in genetic traits that implicate with disease progression led to the investigation of further genetic variants as predictors of cognitive impairment in PD. Klotho longevity gene was found to interfere with cognitive dysfunction, since in PD carriers of the KL-VS haplotype the interval between disease onset and the onset of cognitive impairment was shorter [121]. Single nucleotide polymorphisms (SNPs) of the aquaporin-4 gene (*AQP4*) were also associated to cognitive performance of PD patients; *AQP4* rs162009 SNP was found protective against cognitive decline, relating to better performance in letter-number sequencing test and SDMT; yet, PD patients with *AQP4* rs68006382 SNP demonstrated a faster progression to mild cognitive impairment and worse performance in letter-number sequencing, semantic fluency, and SDMT [122].

Conclusions

Our narrative review aimed to identify appropriate biomarkers of cognitive impairment in PD, detected in CSF and/or blood. Despite contradictory evidence regarding the role of α-synuclein as biomarker of cognitive dysfunction in PD, reported associations with MCI and dementia risk are evident. Research of posttranslational isoforms could provide insights in more appropriate markers of cognitive impairment, utilizing technological advances in immunoassays. Aβ is considered more established as indicator of worse cognition in PD and predictor of cognitive decline, while tau protein was inconsistent in corresponding associations. Ratios between CSF and plasma α-synuclein, Aβ and tau could further explored as cognitive biomarkers, since promising results has been reported [61]. Recently introduced in PD cognitive impairment course, studies of NfL demonstrated that increased CSF and plasma NfL concentrations could be considered reliable biomarker of worse cognitive performance as well as in predicting future cognitive deterioration. Furthermore, inflammatory mediators, oxidative stress markers and growth factors have been systematically related to impaired cognition in PD, reflecting pathophysiological properties in neuronal degeneration and injury.

Genetic predisposition is an independent risk factor for the progressing cognitive dysfunction in PD course, even in idiopathic PD cases. The *APOE* ε4 allele, *SNCA* and *GBA* mutations result in cognitive deficits in multiple domains, with a prognostic value regarding PDD development. *COMT* and *MAPT* polymorphisms could also indicate cognitive impairment, while recent studies revealed cognitive associations for *AQP4* and Klotho genes. Advances in genetic medicine are emerging and future studies could introduce new candidate biomarkers.

Future research is necessary for the validation of the various promising biomarkers, described in our review. Early detection of cognitive deficits as well as the prediction of cognitive decline are key elements for the development of targeted therapeutic interventions. Accordingly, robust biomarkers could be implemented in clinical trials as monitoring estimates.

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Vignettes

1. Highlights

- The present review aims to present recent studies regarding valuable biomarkers of cognitive impairment in PD
- Amyloid β has been established as biomarker of cognitive dysfunction in PD, reliably predicting cognitive decline in longitudinal assessments
- Neurofilament light chain is a promising biomarker
- Markers of neuroinflammation, lysosomal activity and growth factors have been associated with cognitive deficits in multiple domains
- Genetic variants contribute to a higher risk of cognitive dysfunction development

2. Potential of biomarkers in clinical practice

- Robust markers of cognitive function could be used as monitoring biomarkers, assessing the natural disease course as well as the effect of therapeutic interventions
- Prognostic biomarkers could enable earlier interventions in order to hinder the progressing cognitive decline
- Implementation of reliable biomarkers in clinical trials with investigational drugs could provide reliable outcome measures
- A combination of various biomarkers, reflecting different pathogenic processes of cognitive impairment in PD, could facilitate diagnosis and prognostic evaluation of cognitive decline