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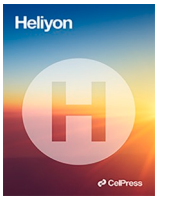

Research article

Unraveling the interplay of β-amyloid pathology and Parkinson's disease progression: Insights from autopsy-confirmed patients

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ABSTRACT

Background: Parkinson's disease (PD) is a prevalent neurodegenerative disorder that manifests with both motor and non-motor symptoms, with α-synuclein misfolding recognized as a key contributor. Cognitive decline in advanced PD stages prompts interest in amyloid deposition, a hallmark of Alzheimer's disease (AD), as a potential factor. This study explores the impact of β-amyloid (Aβ) pathology in PD patients on disease progression, aiming to elucidate the role of Aβ in PD development and progression.

Methods: This study included autopsy-confirmed PD patients with post-mortem analyses from the Parkinson's Progression Markers Initiative. Comprehensive clinical assessments, including demographic data, clinical features, CSF markers, and neuroimaging, were conducted. Statistical analyses assessed differences between groups based on the severity of AD neuropathological changes.

Results: All 16 PD participants exhibited severe Lewy body pathology, with 75 % displaying AD neuropathological changes. At baseline, PD patients with severe or moderate AD neuropathological changes had a lower Aβ42 levels ($p = 0.022$) and Aβ42/tau ratio ($p = 0.001$). Longitudinal follow-up data indicated that individuals with severe or moderate AD neuropathological changes exhibited a more rapid decline in MOCA score and BJLOT score, along with a quicker increase in MDS-UPDRS III score.

Conclusions: The study underscores the presence of severe Aβ pathology in PD, suggesting a role in accelerated disease progression. Cross-seeding between Aβ and α-synuclein may contribute to rapid clinical symptom progression. Further research is needed for a comprehensive understanding of neurodegenerative disease complexities and exploring potential therapeutic interventions targeting protein aggregation.

1. Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, affecting 2–3% of the population aged 65 years

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and older, and it is characterized by the gradual onset of both motor and non-motor symptoms [1,2]. Our current understanding of PD primarily revolves around the degeneration of dopamine-producing neurons located within the substantia nigra region of the midbrain [2]. Within this context, the misfolding of α-synuclein is regarded as a pivotal factor contributing to the pathogenesis of PD [3].

Cognitive decline frequently emerges as a significant issue in advanced stages of PD [4]. There is a prevailing hypothesis suggesting that amyloid deposition, typically considered the hallmark of Alzheimer's disease (AD), contributes to cognitive impairments in synucleinopathies [5]. Several amyloid positron emission tomography (PET) imaging studies have provided evidence of amyloid deposition in individuals with synucleinopathies, including PD, PD with dementia, and dementia with Lewy bodies [6–8]. Further studies have confirmed that individuals who tested positive on amyloid PET scans exhibited the typical presence of diffuse β-amyloid (Aβ) plaques, neuritic plaques, and neurofibrillary tangle pathology [9,10]. This mixed pathology might contribute to a more intricate influence on the presentation of symptoms in patients and the progression of the disease.

However, there is currently a lack of relevant clinical research to explore this intriguing phenomenon. This study aims to include autopsy-confirmed patients for further investigation, exploring the impact of Aβ pathology in PD patients on the progression of the disease, including neuropsychiatric symptoms and motor symptoms, to elucidate the role of Aβ in the development and progression of PD.

2. Materials and methods

2.1. Participants

The data utilized in this study were sourced from the Parkinson's Progression Markers Initiative (PPMI) database. PPMI is an international, multicenter cohort study with the objective of identifying biomarkers linked to the progression of PD [11–13]. The PPMI database encompassed static participant data, clinical presentation history, various non-motor assessments, biospecimen analyses, genetic results, medical history, image data analyses, and more. It followed rigorous protocols for data processing and quality control to ensure data reliability (https://www.ppmi-info.org/). Data collection across sites is standardized with strict adherence to protocols, including clinical assessments and biomarker collection. Clinical data undergo cleaning and outlier detection to maintain accuracy. Data were converted into standardized formats before being made available, ensuring consistency and facilitating downstream analyses. In this study, patients with detail post-mortem analyses were included. The inclusion criteria were an autopsy-confirmed PD diagnosis and the availability of baseline clinical and neuropathological data. The exclusion criteria were primary neuropathological diagnoses other than PD, lacked the presence of Lewy bodies, as well as incomplete clinical, pathological, or follow-up data.

2.2. Clinical assessments

We collected demographic data and clinical features of the participants, including age, sex, body mass index, history of hypertension, and years of education. Disease severity was assessed using the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) score and modified Schwab & England ADL Score (MSEADLG). Olfactory dysfunction was measured by the University of Pennsylvania Smell Identification Test (UPSIT). Sleep disturbances were evaluated with REM Sleep Behavior Disorder Questionnaire Score (RBDQ) and the Epworth Sleepiness Scale (ESS). Depression was evaluated with the Geriatric Depression Scale (GDS). Anxiety was evaluated with the State-Trait Anxiety Inventory (STAI). Cognitive function is evaluated using the Montreal Cognitive Assessment (MoCA) and Benton Judgement of Line Orientation Test (BJLOT). Autonomic dysfunction was evaluated with the Scales for Outcomes in Parkinson's Disease-Autonomic (SCOPA-AUT).

The collection of cerebrospinal fluid (CSF) followed standardized lumbar puncture procedures. The CSF samples were subjected to analysis for total α-synuclein, β-amyloid 1–42 (Aβ42), tau, and Aβ42/tau ratio, as previously described [14,15]. Serum neurofilament light chain was quantified using the Simoa assay [16]. Additionally, data on serum uric acid measurements were collected.

Dopamine transporter (DAT) scan with the DAT tracer 123I-ioflupane was conducted following standard operating procedures at the baseline. Mean putamen binding ratio, mean caudate binding ratio, and mean striatum binding ratio were utilized in this study.

APOE alleles (ε2, ε3, and ε4) were determined utilizing TaqMan Assays or the NeuroX genotyping platform, specifically by examining rs429358 and rs7412 [17]. Further information can be found in the PPMI biologics manual.

2.3. Statistical analysis

The Kolmogorov–Smirnov test was used for normality testing. Continuous variables were presented as the mean ± SD [min - max], while categorical data were presented as frequencies (percentages). Comparisons between two groups were conducted using the independent *t*-test, Mann–Whitney *U* test, or Chi-square test, as appropriate. Two-tailed *p*-values were calculated for all analyses, with a significance level set at 0.05. Statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Neuropathological assessment

This study enrolled 16 individuals diagnosed with PD. As illustrated in Table 1, all participants (16/16) exhibited severe Lewy body pathology, with 81.25 % (13/16) classified in Braak stage VI, and the remaining 18.75 % (3/16) in stage V. Interestingly, among the 16

participants, 12.5 % (2/16) showed severe AD neuropathological changes, 25 % (4/16) exhibited moderate changes, 37.5 % (6/16) displayed mild changes, and 25 % (4/16) showed no AD neuropathological changes. Glial cytoplasmic inclusions were not observed in any of the 14 participants. Limbic-associated TDP-43 encephalopathy was observed in 4 out of 14 participants. Chronic traumatic encephalopathy was not observed in any of the 16 participants.

3.2. Baseline assessment

The demographic and clinical features of all participants were summarized in Table 2. The participants were stratified into two groups according to the severity of AD neuropathological changes: group 1 consisted of individuals with none or mild changes, while group 2 comprised those with moderate or severe changes.

In group 1, the mean age was 66.3 ± 9.4 years, while in group 2, it was 68.2 ± 6.6 years. Both groups had similar baseline characteristics, including age, gender distribution, body mass index, history of hypertension, years of education, and scores on clinical assessments. CSF markers revealed a significant difference in Aβ42 levels between the two groups ($p = 0.022$), with group 1 showing higher levels compared to group 2. However, α-synuclein and tau levels did not significantly differ. The Aβ42/tau ratio was notably higher in group 1 compared to group 2 ($p = 0.001$). Serum markers, including uric acid and neurofilament light chain, showed no significant differences between the two groups. DAT scan data indicated similar mean caudate, putamen, and striatum uptake in both groups. For 193 healthy controls in the PPMI database, with a mean age of 60.8 ± 11.3, DAT scan data showed mean caudate values of 3.0 ± 0.6, mean putamen values of 2.1 ± 0.6, and mean striatum values of 2.6 ± 0.6. *APOE* ε4 allele frequency was higher in group 2 (66.7 %) compared to group 1 (20 %).

3.3. Longitudinal follow-up assessment

In this cohort of 16 participants, the cumulative follow-up duration reached 87 years, with an average follow-up period of 5.5 years. A comprehensive longitudinal follow-up was conducted to document the progression patterns of both motor and non-motor symptoms in these patients (Fig. 1). Through visualizing the follow-up data, we observed that individuals in group 2 exhibited a more rapid decline in MOCA score and BJLOT score, along with a quicker increase in MDS-UPDRS III score. Individuals in group 1 exhibited a quicker increase in GDS score and RBDQ score.

4. Discussion

The post-mortem neuropathological analyses revealed severe Lewy body pathology in all PD participants, with varying degrees of AD neuropathological changes. Baseline analysis indicated significant differences in Aβ42 levels and Aβ42/tau ratio between groups with distinct AD pathology severities, while other demographic and clinical features remained similar. Longitudinal follow-up demonstrated divergent motor and non-motor symptom progression patterns. These findings underscore the complex interplay between AD pathology and PD progression, emphasizing the need for further research to elucidate the mechanisms and potential therapeutic implications of these interactions.

Abnormal Aβ metabolism is regarded as a fundamental aspect in comprehending the pathophysiological mechanisms underlying AD [18]. The assessment of CSF Aβ levels continues to be the most valuable marker for diagnostic purposes and close association with developing new drugs for AD [19–21]. PD patients with severe or moderate AD neuropathological changes had lower Aβ42 levels at baseline in this study. Interestingly, several studies had reported lower baseline CSF Aβ42 levels can predict cognitive impairment in patients with PD [22–25]. Our longitudinal clinical correlation analyses may offer a partial explanation of predictive value of CSF Aβ42 and provide further insights into the potential association between CSF Aβ42 levels and AD neuropathological changes in patients with PD. In addition, previous studies had reported approximately 80 % of PD patients were likely to experience dementia if they survive for 20 years with the condition, with an average prevalence of about 40 % [26,27]. Our neuropathological findings indicate that 75 % of PD patients exhibited AD neuropathological changes, with 37.5 % displaying severe or moderate AD neuropathological changes. This

Table 1
Neuropathology results of post-mortem analyses in PD patients.

	PD patients (n = 16)
Presence of Lewy body pathology, n (%)	
severe	16 (100)
other	0 (0)
Braak stage, n (%)	
stage I - IV	0 (0)
stage V	3 (18.75)
stage VI	13 (81.25)
Presence of Alzheimer's disease pathology, n (%)	
none	4 (25)
mild	6 (37.5)
moderate	4 (25)
severe	2 (12.5)

Table 2
Demographic data and clinical features at baseline.

	Group 1 (n = 10)	Group 2 (n = 6)	*p* value
Age (years)	66.3 ± 9.4 [49.2–77.3]	68.2 ± 6.6 [60.1–75.6]	n.s.
Male, n (%)	6 (60)	3 (66.7)	n.s.
BMI	24.8 ± 4.3 [20.0–31.6]	26.5 ± 5.0 [19.9–33.2]	n.s.
Hypertension, n (%)	2 (20)	2 (33.3)	n.s.
Education (years)	16.2 ± 4.5 [8–24]	17.3 ± 2.0 [14–20]	n.s.
MDS-UPDRS total	42.2 ± 18.5 [17–54]	41.8 ± 14.3 [36–70]	n.s.
MDS-UPDRS I	7.2 ± 6.0 [1–18]	8.3 ± 5.1 [2–16]	n.s.
MDS-UPDRS II	8.2 ± 5.7 [2–17]	6.0 ± 3.3 [2–12]	n.s.
MDS-UPDRS III	26.8 ± 12.2 [14–46]	27.5 ± 9.7 [20–46]	n.s.
MSEADLG	88.0 ± 14.2 [50−100]	87.5 ± 14.1 [60−100]	n.s.
UPSIT	15.3 ± 8.3 [5–32]	13.7 ± 6.1 [7–21]	n.s.
RBDQ	3.3 ± 2.1 [1–8]	6.8 ± 4.3 [1–12]	n.s.
ESS	7.7 ± 4.0 [3–14]	6.7 ± 2.3 [4–10]	n.s.
GDS	2.9 ± 2.7 [0–8]	2.2 ± 2.1 [0–5]	n.s.
STAI	74.4 ± 25.2 [42−112]	66.5 ± 24.4 [43−113]	n.s.
MOCA	26.7 ± 2.4 [22–30]	26.2 ± 3.8 [20–30]	n.s.
BJLOT	11.7 ± 2.3 [8–15]	12.0 ± 2.8 [8–15]	n.s.
SCOPA-AUT	9.8 ± 7.1 [4–22]	8.3 ± 1.9 [6–11]	n.s.
CSF markers			
$A\beta_{42}$	772.5 ± 200.1 [448.2–1006.0]	529.7 ± 130.0 [414.8–674.9]	0.022
α-syn	1172.3 ± 249.4 [856.9–1615.8]	1010.0 ± 229.9 [804.7–1326.1]	n.s.
tau	143.6 ± 40.5 [87.7–217.1]	176.4 ± 60.6 [101.7–244.9]	n.s.
$A\beta_{42}$/tau ratio	5.5 ± 1.0 [3.6–6.6]	3.2 ± 0.9 [1.9–4.5]	0.001
Serum markers			
uric acid	5.1 ± 1.1 [3.6–7.5]	5.0 ± 1.5 [3.6–7.3]	n.s.
NFL	14.5 ± 6.0 [6.7–27.5]	17.9 ± 5.5 [11.3–24.6]	n.s.
DAT scan			
mean caudate uptake	1.6 ± 0.6 [0.4–2.4]	1.7 ± 0.6 [1.2–2.6]	n.s.
mean putamen uptake	0.7 ± 0.3 [0.2–1.2]	0.7 ± 0.2 [0.5–1.0]	n.s.
mean striatum uptake	1.2 ± 0.4 [0.3–1.7]	1.2 ± 0.4 [0.9–1.8]	n.s.
APOE ε4 allele, n (%)	2 (20)	4 (66.7)	n.s.

Group 1, individuals with no or mild pathological feature of Alzheimer's disease; Group 2, individuals with moderate or severe pathological feature of Alzheimer's disease; BMI, Body mass index; MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; MSEADLG, Modified Schwab & England ADL Score; UPSIT, University of Pennsylvania Smell Identification Test; RBDQ, REM Sleep Behavior Disorder Questionnaire Score; ESS, Epworth Sleepiness Scale; GDS, Geriatric Depression Scale; STAI, State-Trait Anxiety Inventory; MOCA, Montreal Cognitive Assessment; BJLOT, Benton Judgement of Line Orientation Test; SCOPA-AUT, Scale for Outcomes in Parkinson's Disease-Autonomic; CSF, cerebrospinal fluid; Aβ42, β-amyloid 1–42; α-syn, total α-synuclein; NFL, Neurofilament light chain; DAT, dopamine transporter; n.s., not significant; Continuous variables are presented as Mean ± SD [min - max].

observation may partially explain the significant occurrence of dementia in PD patients with a prolonged disease condition. Kurkinen et al. discussed other avenues in AD research, including the presenilin hypothesis, synaptic glutamate signaling, and the role of astrocytes and the glutamate transporter EAAT2 in AD development [28]. This is a highly meaningful topic and that further investigation is warranted to determine whether these mechanisms contribute to the progression of clinical symptoms and comorbid pathological processes in PD.

All PD patients included in this study presented severe Lewy body pathology. Notably, those PD patients who also exhibited severe or moderate AD neuropathological changes demonstrated a more rapid progression in both motor and non-motor symptoms throughout the course of the disease. These findings suggest Aβ metabolism may be involved in the disease progression of these PD patients. This also raises the question of whether the co-occurrence of AD pathology and Lewy body pathology is the result of cross-seeding Aβ and α-synuclein, thereby further promoting the aggregation of each other, leading to rapid clinical symptoms progression. In fact, there is increasing attention towards the potential overlap in common pathological pathways between AD and PD. Studies conducted both in vivo and in vitro provided convincing evidence supporting a synergistic interplay between Aβ and α-synuclein deposition, with each promoting the aggregation of the other [29–33]. Hybrid oligomers of Aβ and α-synuclein have been detected in the brains of AD and PD patients, as well as in transgenic mouse models, indicating a direct interaction between these two proteins [34]. Molecular dynamics simulations also predicted the co-aggregation of Aβ and α-synuclein into hybrid oligomers [35]. Externally introduced Aβ42 at sub-lethal concentration induced increased α-synuclein aggregation in neuronal cells [36]. These findings underscore the complex interplay between Aβ and α-synuclein, which may contribute to the progression of neurodegenerative diseases. On the other side, the proportions of amyloid positivity observed across the cognitive spectrum in PD are lower compared to those seen in AD and are more similar with levels observed in elderly controls [37]. This prompts a consideration of whether mild amyloid pathology could also affect PD progression. Due to data limitations, we did not separately analyze PD patients with mild AD pathological features, which will be an important focus for future research.

In addition, given the high prevalence of concurrent Aβ pathology that we observed and its impact on symptoms, it is worth investigating whether the early administration of anti-AD related drugs can improve the prognosis of PD symptoms. Additionally,

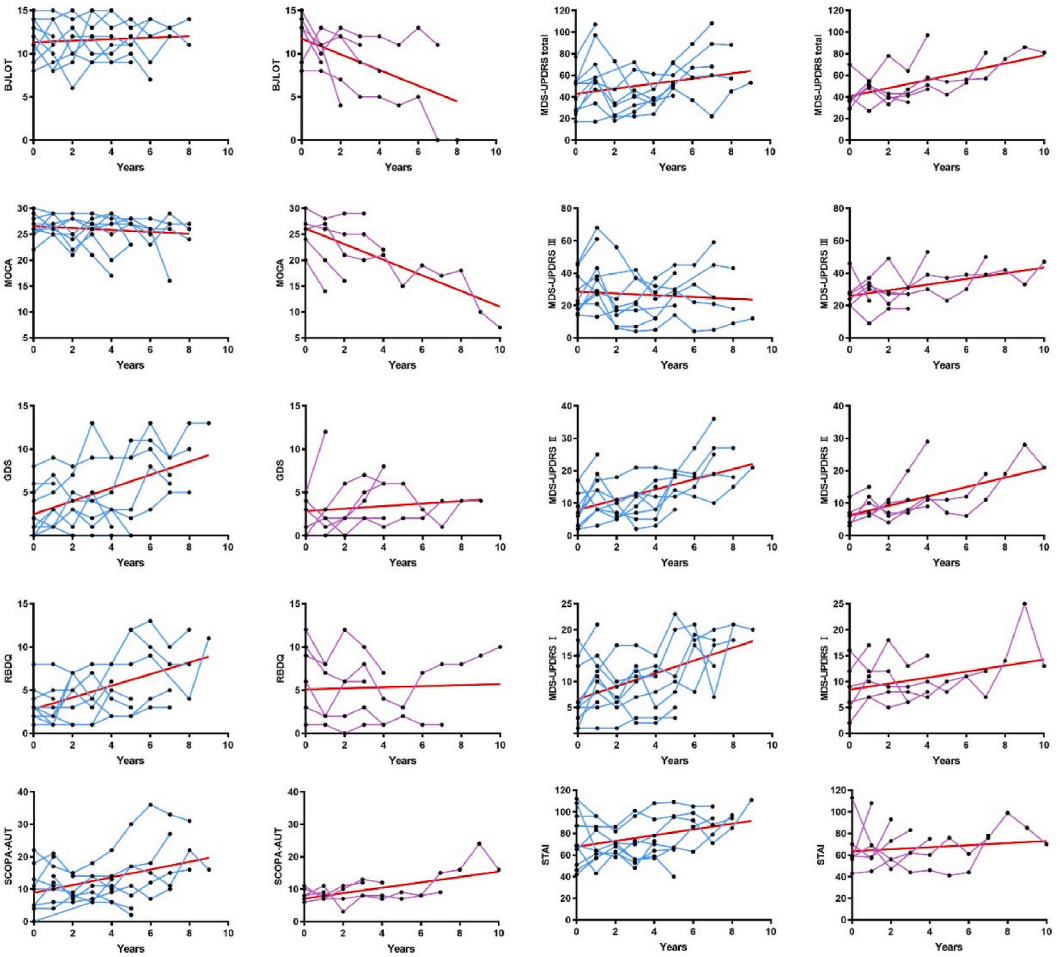

Fig. 1. Progression patterns of motor and non-motor symptoms in PD patients with different Alzheimer's disease (AD) neuropathological changes. Group 1 consisted of individuals with none or mild AD neuropathological changes (blue line), while group 2 comprised those with moderate or severe AD neuropathological changes (purple line).

further research should focus on revealing the mechanisms by which these proteins form disease-associated aggregates and ultimately testing specific anti-protein-aggregation agents.

In this study, there are major limitations that warrant consideration for future research. First, the sample size in this study was relatively small. It may reduce the statistical power of the study, making it difficult to detect subtle effects. The reliance on post-mortem data could introduce selection bias. This limitation suggests the need for larger cohorts and multi-center involvement in future investigations. Second, we solely analyzed the CSF marker data at baseline. The absence of multiple data points limited our ability to explore the longitudinal changes in CSF markers and their dynamic relationship with Aβ pathology over time. Future research should consider a more extensive data collection approach to capture these changes more effectively. Third, we currently lack autopsy data from healthy individuals or PD patients without AD neuropathological changes to establish control groups, which could further confirm our findings. Future research should focus on addressing this point and provide a more detailed understanding of the implications of the association between the observed clinical changes and the underlying pathology.

In summary, our study expands on existing research by examining the impact of Aβ pathology on symptoms progression in PD patients. We analyzed data from autopsy patients with confirmed pathology, and our findings highlight the presence of more severe Aβ pathology in PD patients, which may contribute to an accelerated disease progression. Additionally, this study provides new insights into the complex interactions between AD and PD pathologies. Notably, the cross-seeding of Aβ and α-synuclein may potentially promote the aggregation of each other and leading to rapid clinical symptom progression. This research underscores the complexity of neurodegenerative diseases and calls for a more comprehensive understanding of the interactions between different pathologies, providing a foundation for future studies in this field.

CRediT authorship contribution statement

Linxi Chen: Writing – original draft. **Hongsheng Lu:** Writing – review & editing, Conceptualization. **Lingqun Mao:** Writing – review & editing. **Junxin Lin:** Writing – review & editing, Conceptualization. **Peng Liu:** Writing – review & editing, Validation, Funding acquisition, Data curation, Conceptualization.

Trial registration number

The study was registered at ClinicalTrials.gov as NCT01141023.

Ethical statement

Our study did not require an ethical board approval because this study was based on publicly available data.

Data availability statement

Data used in this study was downloaded from PPMI database.

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Informed consent/patient consent

Patient consents were not required as this study was based on publicly available data.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] R.B. Postuma, D. Berg, M. Stern, et al., MDS clinical diagnostic criteria for Parkinson's disease, Mov. Disord. 30 (2015) 1591–1601.
[2] W. Poewe, K. Seppi, C.M. Tanner, et al., Parkinson disease, Nat Rev Dis Primers 3 (2017) 17013.
[3] J. Estaun-Panzano, M.L. Arotcarena, E. Bezard, Monitoring alpha-synuclein aggregation, Neurobiol. Dis. 176 (2023) 105966.
[4] D. Aarsland, B. Creese, M. Politis, et al., Cognitive decline in Parkinson disease, Nat. Rev. Neurol. 13 (2017) 217–231.
[5] M. Petrou, B.A. Dwamena, B.R. Foerster, et al., Amyloid deposition in Parkinson's disease and cognitive impairment: a systematic review, Mov. Disord. 30 (2015) 928–935.
[6] M. Petrou, N.I. Bohnen, M.L. Muller, R.A. Koeppe, R.L. Albin, K.A. Frey, Abeta-amyloid deposition in patients with Parkinson disease at risk for development of dementia, Neurology 79 (2012) 1161–1167.
[7] S.N. Gomperts, D.M. Rentz, E. Moran, et al., Imaging amyloid deposition in Lewy body diseases, Neurology 71 (2008) 903–910.
[8] J.R. Winer, A. Maass, P. Pressman, et al., Associations between tau, beta-amyloid, and cognition in Parkinson disease, JAMA Neurol. 75 (2018) 227–235.
[9] M.A. Burack, J. Hartlein, H.P. Flores, L. Taylor-Reinwald, J.S. Perlmutter, N.J. Cairns, In vivo amyloid imaging in autopsy-confirmed Parkinson disease with dementia, Neurology 74 (2010) 77–84.
[10] P.T. Kotzbauer, N.J. Cairns, M.C. Campbell, et al., Pathologic accumulation of alpha-synuclein and Abeta in Parkinson disease patients with dementia, Arch. Neurol. 69 (2012) 1326–1331.
[11] K. Marek, S. Chowdhury, A. Siderowf, et al., The Parkinson's progression markers initiative (PPMI) - establishing a PD biomarker cohort, Ann Clin Transl Neurol 5 (2018) 1460–1477.
[12] Parkinson Progression Marker I, The Parkinson progression marker initiative (PPMI), Prog Neurobiol 95 (2011) 629–635.
[13] S.A. Bukhari, K.N.H. Nudelman, M. Rumbaugh, et al., Parkinson's Progression Markers Initiative brain autopsy program, Parkinsonism Relat Disord 101 (2022) 62–65.
[14] G. Pagano, N. Ferrara, D.J. Brooks, N. Pavese, Age at onset and Parkinson disease phenotype, Neurology 86 (2016) 1400–1407.
[15] R. Kim, J. Lee, H.J. Kim, et al., CSF beta-amyloid(42) and risk of freezing of gait in early Parkinson disease, Neurology 92 (2019) e40–e47.
[16] F. Sampedro, R. Perez-Gonzalez, S. Martinez-Horta, J. Marin-Lahoz, J. Pagonabarraga, J. Kulisevsky, Serum neurofilament light chain levels reflect cortical neurodegeneration in de novo Parkinson's disease, Parkinsonism Relat Disord 74 (2020) 43–49.
[17] M.A. Nalls, M.F. Keller, D.G. Hernandez, et al., Baseline genetic associations in the Parkinson's progression markers initiative (PPMI), Mov. Disord. 31 (2016) 79–85.
[18] J.A. Hardy, G.A. Higgins, Alzheimer's disease: the amyloid cascade hypothesis, Science 256 (1992) 184–185.

[19] N. Mattsson, H. Zetterberg, O. Hansson, et al., CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment, JAMA 302 (2009) 385–393.
[20] Y. Zhang, H. Chen, R. Li, K. Sterling, W. Song, Amyloid beta-based therapy for Alzheimer's disease: challenges, successes and future, Signal Transduct Target Ther 8 (2023) 248.
[21] A. Martorana, F. Di Lorenzo, L. Belli, et al., Cerebrospinal fluid Abeta42 levels: when physiological become pathological state, CNS Neurosci. Ther. 21 (2015) 921–925.
[22] A. Siderowf, S.X. Xie, H. Hurtig, et al., CSF amyloid beta 1-42 predicts cognitive decline in Parkinson disease, Neurology 75 (2010) 1055–1061.
[23] S. Lerche, I. Wurster, B. Roben, et al., Parkinson's disease: evolution of cognitive impairment and CSF Abeta(1-42) profiles in a prospective longitudinal study, J. Neurol. Neurosurg. Psychiatry 90 (2019) 165–170.
[24] G. Alves, J. Lange, K. Blennow, et al., CSF Abeta42 predicts early-onset dementia in Parkinson disease, Neurology 82 (2014) 1784–1790.
[25] D.J. Irwin, J. Fedler, C.S. Coffey, et al., Evolution of Alzheimer's disease cerebrospinal fluid biomarkers in early Parkinson's disease, Ann. Neurol. 88 (2020) 574–587.
[26] J.L. Cummings, Intellectual impairment in Parkinson's disease: clinical, pathologic, and biochemical correlates, J Geriatr Psychiatry Neurol 1 (1988) 24–36.
[27] T.A. Hughes, H.F. Ross, S. Musa, et al., A 10-year study of the incidence of and factors predicting dementia in Parkinson's disease, Neurology 54 (2000) 1596–1602.
[28] M. Kurkinen, M. Fulek, K. Fulek, J.A. Beszlej, D. Kurpas, J. Leszek, The amyloid cascade hypothesis in Alzheimer's disease: should we change our thinking? Biomolecules 13 (2023).
[29] Y. Compta, L. Parkkinen, P. Kempster, et al., The significance of alpha-synuclein, amyloid-beta and tau pathologies in Parkinson's disease progression and related dementia, Neurodegener. Dis. 13 (2014) 154–156.
[30] T. Lashley, J.L. Holton, E. Gray, et al., Cortical alpha-synuclein load is associated with amyloid-beta plaque burden in a subset of Parkinson's disease patients, Acta Neuropathol. 115 (2008) 417–425.
[31] L.K. Clinton, M. Blurton-Jones, K. Myczek, J.Q. Trojanowski, F.M. LaFerla, Synergistic Interactions between Abeta, tau, and alpha-synuclein: acceleration of neuropathology and cognitive decline, J. Neurosci. 30 (2010) 7281–7289.
[32] E. Masliah, E. Rockenstein, I. Veinbergs, et al., beta-amyloid peptides enhance alpha-synuclein accumulation and neuronal deficits in a transgenic mouse model linking Alzheimer's disease and Parkinson's disease, Proc Natl Acad Sci U S A. 98 (2001) 12245–12250.
[33] O. Pletnikova, N. West, M.K. Lee, et al., Abeta deposition is associated with enhanced cortical alpha-synuclein lesions in Lewy body diseases, Neurobiol. Aging 26 (2005) 1183–1192.
[34] I.F. Tsigelny, L. Crews, P. Desplats, et al., Mechanisms of hybrid oligomer formation in the pathogenesis of combined Alzheimer's and Parkinson's diseases, PLoS One 3 (2008) e3135.
[35] M. Iljina, A.J. Dear, G.A. Garcia, et al., Quantifying Co-oligomer formation by alpha-synuclein, ACS Nano 12 (2018) 10855–10866.
[36] U. Sengupta, R. Kayed, Amyloid beta, Tau, and alpha-Synuclein aggregates in the pathogenesis, prognosis, and therapeutics for neurodegenerative diseases, Prog Neurobiol 214 (2022) 102270.
[37] T.R. Melzer, M.R. Stark, R.J. Keenan, et al., Beta amyloid deposition is not associated with cognitive impairment in Parkinson's disease, Front. Neurol. 10 (2019) 391.