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REVIEW

Amyloid and Tau Co-pathology in Parkinson Disease and Atypical Parkinsonism

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Abstract

Purpose of Review We performed a narrative review of the literature of amyloid and tau co-pathology in Parkinson Disease and atypical parkinsonism in Pubmed database, including articles published between January 2020 to July 2025.

Recent Findings In the last decade, different multicenter research efforts have worked to improve the accuracy of clinical-pathological diagnosis in neurogenerative disease. In this search, growing evidence from neuropathology, neuroimaging and fluid biomarkers have highlighted the role of Alzheimer's disease (AD) co-pathology in Parkinson's disease (PD) and atypical parkinsonism (AP) disorders potentially affecting progression, motor phenotype and cognitive status. Regarding studies of structural and functional imaging evidencing the presence of Amyloid-β (Aβ), tau, as co-pathologies contribute to α-synuclein-related profile of cortical atrophy, network disruption, as well as clinical heterogeneity in PD and AP disorders. In AP fluid biomarkers have shown limited diagnostic accuracy.

Summary Neuropathological evidence from systematic post-mortem surveys confirmed that diffuse and neuritic Aβ plaques are uncommon in non-demented PD (10%), intermediate in PD-dementia (30–40%), and frequent in Dementia with Lewy Bodies (60–80%). The evidence in PD and DLB showed that Aß fluid biomarkers may predict clinical trajectory and cognitive decline, while Aβ-imaging would help stratifying patients and directing therapeutic pipeline designs. In AP disorders, including progressive supranuclear palsy and corticobasal degeneration, a combined multimodal assessment of molecular imaging, structural and functional magnetic resonance with fluid biomarkers shall guarantee future differential diagnosis and prediction of clinical outcomes. Although there are no currently accepted biomarkers for PD or AP, the recent design of plasma tau biomarkers and seed-amplification assays are promising approaches which are also reviewed here.

Keywords Co-pathology · Atypical parkinsonism · Parkinson disease · Fluid biomarkers · Amyloid · Tau

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Introduction

Recent evidence from brain bank and longitudinal cohort data, neuroimaging and biomarkers' research highlights the role of Alzheimer's disease (AD) co-pathology in Parkinson's disease (PD) and atypical parkinsonism (AP) disorders. Two of the diseases included as AP disorders, namely dementia with Lewy body (DLB) and multiple system atrophy (MSA), are considered neuropathologies associated with α-synuclein (αSyn) histopathological lesions, whereas the other two, progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), are neurodegenerative conditions associated with pathological 4-repeat tau lesions. Growing evidence of co-pathologies in these neurodegenerative diseases has emerged and is guiding biomarker development with the hope that these can help distinguish syndromes with overlapping clinical features or due to diverse neuropathology. Hence, the search for co-pathologies in patients manifesting with atypical phenotypes is becoming a common practice when the clinical diagnostic uncertainty is high, as it is stated that vascular co-pathology or amyloid neuropathology in patients with DLB might associate with faster progression rates of cognitive and functional decline (see evidence below).

By definition, the presence of co-pathology or mixed pathological findings is a common feature of older brain tissue. Several studies have shown that the prevalence of mixed pathologies increases with age, with one report finding that 36% of patients with dementia held three or more abnormal (misfolded) protein for instance [1]. However, the process of diagnosing a neurodegenerative disease includes the staging of lesions found in confirmed-autopsy cases following specific framework and criteria (Thal phase, Braak staging and CERAD for AD neuropathological change (ADNC), Braak stage for Lewy body diseases (LBD), and so on). In this line, two scenarios are important to note: first, the sole presence of misfolded proteins detected by immunohistochemistry assays in brain tissue, or its estimation in biochemical assays of peripheral samples (i.e. fluid biomarkers) or by radio-tracer uptake imaging (positron emission tomography, PET) may not be sufficient nor equivalent to the findings conforming a moderate-to-severe stage of a certain neuropathology. A clear example of this can be drawn from the pathological findings of corticobasal syndrome (CBS): while numerous studies have compared AD biomarker-positive CBS to AD biomarker-negative CBS [2–5], only post-mortem examination can truly evaluate whether AD is the primary pathology (CBS-AD) or just a co-pathology (i.e. CBS caused by CBD with secondary ADNC) in a given patient. Second, in the presence of more than one neuropathology, the primary pathology should be hierarchically the one that explains better and fits the clinical presentation of the case while in life.

While co-pathology can be clinically suspected when symptom onset occurs at late age, biomarker interpretation becomes more relevant when facing a younger patient with progressive neurological disease. The goal of this review is to summarize the evidence of copathology in Parkinson and atypical parkinsonism syndromes, highlighting its relevance for both clinical management and biological plausibility of findings of the newest diagnostic techniques.

Evidence of Co-pathology from Neuropathology Standpoint

The neuropathologies with abnormal deposits of αSyn are PD, DLB, and MSA. The differences in abnormal deposits of αSyn among those disorders are based on cellular localization, inclusion types, filament structure, and pathological effects [6]. The intracellular aggregates differ also in their secondary structure (higher proportion of β-sheet pleated αSyn in LB of PD neurons compared with the αSyn of glial cytoplasmic inclusions in oligodendrocytes of MSA), distinct responses to proteolytic agents, conformation of fibrils, seeding activity kinematics, and filaments ultrastructure [7–9]. However, for several years it has been known that αSyn is not the only protein found in intracellular deposits. Within Lewy body disorders, β-amyloid (Aβ) deposition is increasingly recognized as a critical modifier of phenotype and prognosis in PD, Parkinson's disease dementia (PDD) and DLB. Autopsy and in-vivo studies converge on three key observations: (i) Aβ prevalence rises stepwise from PD to PDD and peaks in DLB; (ii) higher Aβ burden accelerates cognitive decline and shifts the clinical picture toward an amnestic–executive profile; and (iii) Aβ interacts synergistically with both tau and αSyn, amplifying neurodegeneration.

Tau protein is a natively unfolded microtubule-associated protein crucial for microtubule assembly and stabilization, primarily found in neuronal axons but also in dendrites. It is involved in microtubule assembly and stabilization, helping transport nutrients and signals efficiently. The expression of the microtubule-associated protein (*MAPT*) gene, which encodes tau, has a complex regulation that involves genetic and epigenetic factors [10]. Six distinct tau isoforms co-exist in brain cells produced by alternative splicing of the gene categorized by the presence of N-terminal repeats and MT-binding repeats (3R or 4R) present in exon-10 [11]. Post-translational modifications of tau, such as phosphorylation and acetylation, significantly affect its aggregation and function. Over 80 potential phosphorylation sites exist on tau, with hyperphosphorylation state that promote aggregation, as documented in secondary tauopathies like AD, and primary tauopathies such as PSP, or CBD [12, 13].

With those concepts in mind and acknowledging that converging evidence supports co-pathology as a common and clinically relevant pathophysiological event in PD and AP syndromes, we review the most recent literature.

Methodology

We performed an narrative review of the literature including articles published between January 2020 to July 2025, in English, Spanish, and Portuguese. Pubmed database searches included the terms: "Co-patholog*" OR "copatholog*" OR "comorbid*" OR "concomitant" OR "mixed patholog*" OR "mixed neurodegenerat*" OR "mixed proteinopath*" OR expression "Amyloid/" OR expression "amyloid.mp." OR "Cerebral Amyloid Angiopathy/" OR "Abeta*.mp." OR expression "Alzheimer Disease/ or Alzheimer*.mp.") combined with (AND) ("Parkinson" OR "Parkinson's" OR "Parkinson's disease" OR "Parkinson disease" OR "parkinsonism" OR "Corticobasal.mp." OR expression "Corticobasal Degeneration/" OR expression "dementia Lewy body" OR expression "Lewy body disease" OR expression "progressive supranuclear palsy") AND (expression "plasma biomarkers" OR "neuroimaging" OR expression "positron-emission tomography" OR expression "magnetic resonance" OR "p-tau" OR expression "phosphorylated tau" OR expression "p tau" expression "ptau*" OR expression ""). Data was included from cross-sectional studies, longitudinal observational cohorts, assessment of clinical trial populations, and a meta-analysis. Additionally, we included studies of recent seeding amplification assays and small case series from academic brain banks.

Evidence of Co-pathology From Current Biomarkers Standpoint

The use AD biomarkers has been available for several years now, but the design of new PET- radioligands [14] that bind to cerebral amyloid and tau, or the phosphorylated-tau species detected in plasma has been propelled by recent cohort studies [15]. Derived from the proposed framework for biological definition of AD [16], although not absent of controversies (see below) [17], these biomarkers now are used as in-life estimators of brain co-pathology. In recent years, the development of seed amplification assays (SAAs), like Real-time Quaking-Induced Conversion (RT-QuIC) or by Protein Misfolding Cyclic Amplification (PMCA) have consistently shown the presence of abnormally misfolded proteins such as αSyn which are competent of in-vitro abnormal seeding monomers of a human recombinant αSyn substrate. These have been developed and tested in CSF, blood, saliva, and skin, salivary glands and colon mucosae [18]. These αSyn-SAA have been proposed as reliable diagnostic markers of the pathological protein with modest to high measures of accuracy, sensitivity and specificity [19]. A positive αSyn-SAAs provides a binary result (yes/no) proposed as a marker of PD-status, however, it does not inform on the biology state of the disease (i.e. severity, prognosis). In the PD's field, αSyn-SAAs has shown different "seeding dynamics" that would potentially allow for the differentiation of PD from AP such as MSA, and PSP [20, 21]. A similar SAA has been developed for phosphorylated-tau and other proteins responsible of neurodegeneration (TAR-DNA binding protein, TDP-43) [22].

Fluid Biomarkers of Amyloid and Tau in PD and AP

Although in the AD field biomarkers play a decisive role in diagnosis, prognosis, and inclusion criteria for clinical trials of disease-modifying therapies [23], there are no currently accepted biomarkers for PD or atypical parkinsonism. This might be due primarily to variability of study design, patient selection, and technical diversity of detection methods. Despite that, several recent studies have used biomarkers in plasma and cerebrospinal fluid as proxies of pathological proteins, suggesting they can help identifying associations and trajectories of co-pathology. Although in LBD the use of CSF and plasma biomarkers is not yet widely standardized in terms of methodology or outcomes, association of plasma biomarkers and AD co-pathology in synucleinopathies is supported by autopsy-confirmed studies. The utility of AD biomarkers in CSF and plasma in characterizing disease progression and cognitive decline in PD was studied within the PPMI (Parkinson's Progression Markers Initiative), a cohort including early-stage PD patients and healthy controls (HC). CSF levels of αSyn, Aβ42, total tau (t-tau), and p-tau were consistently lower in PD. Plasma neurofilament light chain (NfL) levels increased over time [24–26] and were the best independent predictor of disease progression and cognitive decline in PD (AUC = 0.65) [27]. Irwin et al. [24] showed 31.5% of PPMI patients had pathologically decreased CSF Aβ42 levels at baseline, reduced p-tau, and t-tau. Baek et al. [25] evaluated these longitudinal biomarkers in PD, finding a progressive decline of CSF αSyn and Aβ42, increased t-tau, and p-tau in PD-MCI. Low baseline Aβ42 predicted faster neurodegeneration, supporting amyloid-related modulation of biomarkers' trajectory and cognitive decline in PD. Similarly, a longitudinal study evidenced reduced Aβ42 and elevated plasma p-tau181 and p-tau231 in PD [27].

Supporting the prognostic role of biomarkers, a prospective 10-year follow-up study by Bäckström et al. [28] identified that higher CSF-NfL and lower Aβ42 predicted conversion to PD dementia (PDD, AUC = 0.86). Tufekcioglu

et al., evidenced that low CSF Aβ42 levels at baseline may indicate comorbid pathology [29]. Chen et al. [30], found plasma αSyn and t-tau levels significantly elevated in PD patients that correlated with Mini Mental State Examination (MMSE) scores and were independent predictors of cognitive impairment, while Aβ42 levels remained unchanged or decreased [30]. Moreover, biomarker progression appeared to differ by motor phenotype: in non-tremor PD Aβ42 levels decreased over two years [26]. This subtype-specific trajectory highlights the importance of motor phenotype in CSF biomarker dynamics. In this line, a cross-sectional study [31] found higher CSF Aβ42 in PD with freezing of gait (PD-FOG) and p-tau181 decreased in both PD with and without FOG. Aβ42 showed a positive correlation with disease duration in PD-FOG but negatively associated in non-FOG PD patients, suggesting a distinct amyloid trajectory in FOG pathophysiology. In contrast, a 2-years follow up found no association between p-tau181 levels and cognition suggesting a limited relevance for cognitive prognosis [32]. Together, these findings highlight the role of low CSF Aβ42, and elevated NfL as early markers of both cognitive and motor decline in PD, and, importantly, that biomarkers' trajectories are influenced by cognitive status, APOE-genotype, and motor phenotype. Although tau biomarkers show inconsistent associations with disease progression, their combined use with Aβ42 and NfL may improve predictive power. Importantly, several studies reported that AD-derived biomarker thresholds may underestimate pathology in PD contexts [24, 25, 28], indicating the need for PD-specific cutoffs. Despite some inconsistencies, particularly regarding plasma tau species, the convergence across studies suggests that integrated biomarker profiling may enhance stratification and prognostication in PD [24–32].

Regarding specific tau biomarkers performance in DLB, ptau217 and ptau181 correlate inversely with CSF $A\beta_{42}$ and accurately flag the presence of ADNC in DLB [33, 34]. Specifically, plasma ptau181 was higher in DLB cases with intermediate/high ADNC, however, it did not correlate with Lewy body Braak stage or tau-PET uptake. Plasma pTau181 in DLB differentiate A+T+ LBD from A–T– with 91% accuracy. Another study found plasma GFAP, but not p-tau181, elevated in LBD with concomitant ADNC [35]. Tau in the cerebrospinal fluid of PD patients has also been widely documented and would reach similar diagnostic performance as evidenced by the recent results of the BIOFINDER-2 cohort where plasma p-tau_{217} had an AUC 0.88 for detecting amyloid-positive DLB cases, suggesting good predictive accuracy for AD co-pathology [33]. Cohort studies without neuropathology-confirmed diagnoses detected changes in biofluid AD-biomarkers, such as higher baseline plasma pTau181 [36], and $A\beta_{42}$/tau ratio [37] in DLB. Elevated CSF-tau and reduced $A\beta_{42}$ were associated with cognitive impairment in PD patients [38], with axial non-dopaminergic symptoms in LBD [39] whereas plasmatic tau levels associated with cognitive status and with its faster annual decline [30, 40–42]. Finally, higher plasma p-tau181 and lower Aβ42−40 ratio predicted conversion from to DLB in idiopathic REM sleep behavior disorder (iRBD) patients with a high negative predictive value (NPV = 96.5%; [43]).

In PSP and CBS, a large clinicopathological cohort [44] (n = 349) studied the relationship between AD status and blood biomarkers in non-AD syndromes. Plasma p-tau217 distinguished intermediate or higher ADNC with excellent accuracy (AUC = 0.95). In MSA patients compared with LBD and tauopathies, Koníčková et al. [45] found that CSF biomarker ratios such as t-tau/α-syn, t-tau/p-tau, and neurofilament heavy-chain were elevated, however, with a limited diagnostic specificity. Other studies observed no differences in serum p-tau181 in PSP [46].

Neuroimaging of Amyloid and Tau in PD and AP

Studies of structural and functional imaging have demonstrated how Aβ, tau and αSyn co-pathologies contribute to cortical atrophy, network disruption, and clinical heterogeneity in PD and AP disorders. For instance, in LBD, emerging evidence points to a synergistic interaction between Aβ and αSyn proteins. The presence of cortical Aβ deposition has been evidenced by retention of the Pittsburgh compound B positron emission tomography (PiB-PET). Elevated PiB-PET uptake in DLB and cognitively impaired PD participants was linked with more widespread cortical thinning in medial temporal regions (a signature of AD pathology). Notably, atrophy in the subiculum and CA1 (known AD-vulnerable areas) in LBD appears to be accelerated by tau and related to cognitive impairment, reinforcing the AD-related neurodegeneration hypothesis and supporting the concept of in-vivo pathological staging of AD co-pathology in patients LBD [47]. Another study, carried out by Duong et al. [48] in a cohort of mixed LBD and AD cases, reported that patients who were both Aβ-positive and α-synuclein-positive exhibited a distinct posterior parieto-occipital pattern of hypometabolism on fluorodeoxyglucose (FDG)-PET. Structural magnetic resonance imaging (MRI) can also capture underlying AD co-pathology in PD and AP syndromes by identifying atrophy patterns characteristic of AD. Colloby et al. [49] examined cortical thickness across AD, dementia with Lewy bodies (DLB), and Parkinson's disease dementia (PDD). The gradient of cortical atrophy might reflect the additive effect of AD pathology on the Lewy body pathology-related neurodegeneration. In the ADNI cohort, Silva-Rodríguez et al. [50] demonstrated that amnestic patients with dual AD and LB biomarker signatures exhibited more severe temporo-parietal hypometabolism

and declined faster than pure AD cases. In a large imaging cohort ($n=4549$), DLB with a Aβ+in CSF showed more medial temporal atrophy MTA than those with a negative CSF-Aβ, independently of white matter hyperintensities or p-tau levels, which indicates a DLB-specific relationship between Aβ and MTA [51]. Those findings suggest a continuum of atrophy, with DLB showing intermediate patterns between PDD and AD.

AD biomarkers also shed light in AP. Garcia-Cordero et al. [2] examined patients with CBS and PSP with and without underlying AD pathology as measured by fluid biomarkers. CBS and PSP patients with AD pathology showed atrophy in AD signature regions (i.e. temporal and parietal cortices) and disconnection (measured by functional connectivity resting-state-MRI, rs-fMRI) of the default mode network (typically affected in AD patients) compared to those without AD-biomarkers. All that evidence highlights the potential role of neuroimaging-based models that integrate atrophy patterns with the spatial distribution of co-pathologies and specifically disconnected networks in helping to distinguish co-pathologies profiles in PD and AP disorders. However, discrepancies may emerge in certain syndromes, as specific features can potentially mask or confound the underlying pathology. For example, Ando et al. [52] reported a case of CBD that presented with the hot cross bun sign, an imaging feature typically associated with multiple system atrophy (MSA). Carlos et al. [53] demonstrated that distinct patterns of FDG-PET and tau-PET uptake may help in the antemortem differentiation of MSA mimicking PSP from true PSP. Another example is the discordant clinical> biological staging in atypical presentations such as LBD, PSP, and CBD cases, often in the context of vascular disease, αSyn positivity, or TDP-43–like atrophy patterns [54].

The presence of co-pathologies affects both brain structure and function as observed on neuroimaging and also contributes to heterogeneity in the clinical presentation. In a post-mortem study, Colloby et al. [55] demonstrated that the distribution of tau, Aβ, and αSyn varies significantly across AD, DLB, mixed-dementia, and PDD groups, with distinct spatial patterns corresponding to motor and cognitive symptoms. The distribution of αSyn pathology was linked to motor dysfunction and hallucinations, while Aβ and tau pathology followed patterns more typical of AD. In another study, Donaghy et al. [56] provided longitudinal evidence that Aβ positivity in DLB is associated with more rapid cognitive and functional decline. These findings align with prior results that Aβ pathology is a critical driver of clinical deterioration in LBD. Meta-analysis of ^{11}C-PiB studies indicates that the proportion of Aβ-positive scans is ≈5% in PD with mild cognitive impairment (PD-MCI), 34% in PDD and 68% in DLB [57]. Newer tracers corroborate those estimates: Mihaescu et al. [58] showed that regional ^{18}F-florbetaben uptake predicted 49% of Montreal cognitive assessment (MoCA) variance in PD, especially when plaques clustered in the gyrus rectus, anterior cingulate and right parietal cortex. Garcia-Cordero et al. [2] showed that CBS/PSP patients with biomarkers of AD-pathology presented less severe motor symptoms, although similar cognition to those CBS/PSP with negative AD-biomarkers. Adopting a multimodal approach (incorporating fluid biomarkers, PET imaging, and MRI) would improve the diagnostic certainty and inform prognosis in mixed neurodegenerative conditions.

Neuropathological Evidence and Clinical-pathological Correlations of Aβ and Tau in PD

Amyloid Co-pathology in PD

This section summarizes the recent literature while integrating seminal earlier reports that established the field. From a diagnostic standpoint, incorporation of Aβ status into biological definitions of PD is under discussion, mirroring the recent AT(N) framework revision in AD [54]. Neuropathological evidence from systematic post-mortem surveys confirmed that diffuse and neuritic Aβ plaques are uncommon in non-demented PD (≈10% of brains), intermediate in PDD (30–40%), and frequent in DLB (60–80%) [57, 59]. Quantitative image-analysis has shown a rostro-caudal gradient, with highest cortical loads in temporal pole, posterior cingulate and orbitofrontal regions. In PDD, moderate plaque density often co-localized with LBD-Braak stages 5–6, whereas in DLB widespread Aβ is accompanied by both neocortical Lewy bodies and higher tau tangle stages. Importantly, the odds of dementia in PD rise 1.5- to 1.7-fold per Thal phase increment of Aβ, independent of αSyn stage [59]. A recent autopsy series aligned with these findings reported that PD patients harboring severe ADNC had faster motor progression and earlier death [60].

Clinicopathological correlation evidence supports that Aβ co-pathology is not an epiphenomenon but a quantitatively and clinically meaningful driver of heterogeneity within Lewy body disorders. The presence of Aβ co-pathology amplifies cognitive and motor deterioration across the spectrum of LBD [61], leading to greater functional loss (-3 points/year in MMSE), and over a 3-fold increase in mortality rates [62]. The approval of anti-Aβ monoclonal antibodies (lecanemab, donanemab) for early AD raises obvious questions for the management of people with diagnosis of synucleinopathies and Aβ-positive biomarker findings. Although no phase III trials have yet targeted this subgroup,

stratification by plasma or PET Aβ is increasingly proposed in disease-modifying studies [63]. Observational data suggest that approximately one-third of PDD and two-thirds of DLB patients would meet current Aβ-positive inclusion thresholds. Given the mixed-pathology landscape, combination strategies that address αSyn (e.g., antisense oligonucleotides, immunotherapy) alongside Aβ may ultimately prove necessary. Routine assessment of Aβ by biofluid or PET biomarkers therefore may hold value for prognosis, trial design and, potentially, therapeutic decision-making in the near future.

Tau Co-pathology in PD

In 1999 Arima et al. [64], found the co-localization of phosphorylated tau and αSyn epitopes in Lewy bodies (LBs) in brain samples from patients with PD and DLB. This was observed more frequently in DLB than in PD. Subsequently, other studies confirmed and deepened these findings, demonstrating the presence of co-pathology in Lewy bodies obtained from brain tissue of patients with DLB [65] with a similar pattern of the one found by Arima, particularly located in the locus coeruleus and basal nucleus of Meynert. An 8-years follow-up study of early-stage PD analyzed ptau181 and t-tau in CSF [66] with results of: (i) lower levels of ptau181, t-tau, and ptau181/t-tau ratio compared to healthy controls that remained stable over 5 years; (ii) baseline ptau181, t-tau and ptau181/t-tau ratio associated with faster motor and cognitive deterioration, and correlated with αSyn, suggesting a potential interaction; but (iii) did not associate with nigrostriatal dopaminergic degeneration measured by dopamine transporter (DAT) imaging. In spite of CSF-tau biomarkers showing low accuracy for distinguishing early-PD patients from controls, and a controversial interaction with αSyn without evidence of dopaminergic denervation, the authors proposed a potential role for these biomarkers in assessing disease progression in early PD.

In skin samples from individuals with neuropathologically confirmed AD, PD, MSA and DLB, Wang et al. [67] used an RT-QuIC assay developed to measure misfolded tau (tau-SAA). They found tau-SAA in PD skin samples were lower than those observed in AD but higher than in normal controls. This was supported by another study found that the prevalence of positive tau in skin biopsies of patients with synucleinopathies is low (10%, for PD and DLB) or absent (for MSA) compared with patients with tauopathies (AD, PSP, and CBD) [68].

In terms of pathological tau within nigrostriatal degeneration, a recent study found tau aggregates present in brain from subjects with minimal motor deficits (MMD), MMD with incidental (in-life asymptomatic) Lewy pathology (MMD-LB) [69]. This higher pathological tau in what the authors consider early stages of α-synuclein-neuropathology (MMD and MMD-LB) compared to PD brains, ranged from small punctate granules to dense neuronal inclusions, insoluble to proteinase-K, and were found spatially distant from αSyn aggregates. Although both 3R and 4R tau isoforms were present in the nigrostriatal system (4R-tau predominant), the authors do not discuss the possibility of those being part of primary ageing-related tauopathy (PART) which is the most common incidental neuropathology with combined 3R/4R tau-aggregates in the basal forebrain [70]. Additionally, the tau aggregates were found in several PD brains even in the absence of αSyn pathology, which has been reported as PART in PD brains [71]. Although the authors suggest that tau may play a role in dopaminergic neuronal degeneration of brain with synucleinopathies and that in later stages of PD, tau and αSyn may co-exist potentially accelerating neurodegeneration, data lacked a direct verification of that hypothesis. Instead, it was mostly challenged by the finding of decreased tau in PD brains with dopaminergic neurons loss.

Aß and Tau in Atypical Parkinsonism Disorders

Amyloid Co-pathology in CBD and PSP

CBS is a pathologically heterogeneous syndrome. While CBD is the most common underlying pathology for this syndrome (representing 30–50% of cases), AD, PSP, and more rarely, other proteinopathies (TAR DNA-binding protein 43, fused-in sarcoma) can also cause CBS [72]. This may lead to challenges for the assessment of co-pathologies in-vivo, as only postmortem examination can clearly disentangle primary pathology and co-pathology. Therefore, in this section we will focus on Aß co-pathology in the context of pathologically confirmed CBD. Interestingly, while both CBD and AD pathologies can independently lead to the same syndrome, there is little evidence that these proteinopathies interact. Studies that explicitly described co-pathology prevalence in CBD cohorts have typically reported low levels of Aß pathology (Table 1). In one of the first large-scale investigations on concomitant pathologies in neurodegenerative disease ($n=766$), 41% of the CBD cohort ($n=29$) showed some degree of Aß aggregation, but only 10% had intermediate to severe Aß pathology [73, 74], similar to a more recent report [75]. In the UK-Biobank dataset, out of 82 patients with confirmed CBD, only 3.7% met criteria for a secondary diagnosis of AD and an additional 14.6% presented with AD features [75]. Maldonado-Diaz et al. [76] even reported a negative correlation between ADNC scores and CBD diagnosis in a cohort of

Table 1 Summarized relevant information of the literature reviewed on copathology in Parkinson's and atypical parkinsonism.

Citation	Sample characteristic	Pathology: y/*n*	Copathology studied / found	Type of evidence*
Dementia with Lewy bodies (DLB)				
Delva et al. 2025 [43]	158 iRBD, 32 converted to: DLB (18), PD (13), MSA (1)	N	Plasma Aβ42/40 ratio and ptau181 can predict conversion to DLB in iRBD	2
Alam et al. 2023 [122]	91 DLB treated with neflamapimod (46) or placebo (45)	N	Pre-treatment plasma ptau181 in DLB. Absence of copathology (normal plasma p-tau181) is associated with better treatment response	2
Diaz-Galvan et al. 2024 [123]	15 iRBD, 37 MCI-LB, 70 DLB	Y	Abnormal Aß PET, tau PET, and plasma p-tau181 values were detected in individuals at different stages of DLB continuum	1, 2
Bolsewig et al. 2024 [41]	342 DLB, 89 HC, 131 AD	N	CSF Aβ was assessed in 101 subjects and positive in half of them. Plasma Aβ42/40 were also higher than in CN.	2
Donaghy et al. 2022 [124]	27 DLB	N	Plasma Aβ42/40 and p-tau181. Lower plasma Aβ42/40 associated greater decline	1,2
Ye et al. 2020 [133]	21 DLB, 16 PD-MCI/PDD, 24 PD-NC	N	Abnormal Aß PET associated with cortical thinning of the medial temporal lobe in DLB and PD-MCI/PDD	1
Donaghy et al. 2020 [56]	28 DLB	N	Aß deposition associated greater 1-year decline (MMSE, functionality)	1, 2, 5, 6
Tan et al. 2025 [62]	Systematic review	Y	AD in LBD associated with faster cognitive/functional decline, mortality, and reduced treatment response	6
Vrillon et al. 2024 [37]	104 DLB, 76 AD, 27 NC	N	Plasma p-tau181 can contribute to identify Aβ copathology in DLB	2
Ye et al. 2025 [34]	53 LBD including 24 with neuropathology, 129 HC, 67 AD	Y	Plasma pTau181 predicted Aβ status on Aβ PET or neuropathology in LBD	1, 2
Rosen et al. 2025 [113]	887 pathologically confirmed AD with amnestic presentation	Y	52/83 of participants meeting criteria for Aducanumab had LB copathology, 4/83 had another tauopathy	1, 2, 6
Coburn et al. 2022 [116]	2 young-onset dysexecutive AD	Y	Young-onset AD phenotypes are associated with LBD co-pathology	1, 5, 6
Cousins et al. 2023 [35]	19 αSyn-AD (+), 30 αSyn-AD (-)	Y	Plasma ptau181 did not associated with AD pathological features in LBD spectrum although GFAP was	2
Rennie et al. 2024 [51]	708 AD, 331 DLB, 1489 MCI, 268 mixed dementia, 148 VascD, 120 PDD, 1505 NC	N	CSF Aβ42 and p-tau 181 were positive in 33% and 37% of DLB respectively	2
Duong et al. 2024 [48]	19 LBD, 47 mixed LBD+AD, 99 AD, 81 MCI/AD due to other causes	Y	Reduced glucose metabolism in LBD>>AD copathology (NFTs)>>atrophy mismatch proposed as AD+LBD biomarker	5
Abdelnour et al. 2024 [36]	114 AD, 274 CN, 94 DLB-NC, 83 DLB with abnormal cognition	N	pTau181 is largely concordant with AD pathological features, and with CSF and PET AD biomarkers: promising biomarker for concurrent ADNC and amyloidosis in DLB. It also predicts cognitive decline in DLB	1, 2
Colloby et al. 2020 [49]	76 AD, 65 DLB, 29 PDD, 76 HC	N	Cortical thickness: intermediate atrophy in DLB (between AD and PDD) that reflects AD co-pathology	1
Pichet Binette et al. 2025 [34]	BioFINDER: 91 CN, 124 subjective cognitive impairment, 270 MCI, 353 dementia ADNI: 380 Aβ+participants	Y	Discordance between clinical and biological AD stage, where symptoms are worse than expected relative to PET AD biomarkers (51% of the sample), associated with more co-pathologies. Among 83 participants with moderate cortical tau but worse clinical stage were: 27 LBD, 5 PD, 6 PSP/CBD	1, 4, 6
Parkinson disease / Parkinson disease dementia (PD / PDD)				
Martinez-Valbuena et al. 2024 [19]	Skin 4R-tau SAA: 6 PD, 7 PSP, 6 MSA, 2 CBD Cervical biopsy 4R-tau SAA: 19 PD, 48 PSP, 18 MSA, 5 CBS, 19 HC	Y	No PD was positive for 4R-tau on either the skin or the cervical biopsy. 1/18 MSA positive on the cervical biopsy 4R-tau SAA.	2, 3, 5
Cristiani et al. 2024 [46]	43 PD, 27 PSP, 39 HC	N	Serum ptau181 in PSP and PD	2, 6
Pilotto et al. 2024 [27]	136 PD, 76 HC	N	Higher plasma p-tau181, p-tau231, and lower Aβ42, in PD	1, 2, 3,4, 5
Colloby et al. 2025 [55]	47 AD, 25 DLB, 20 mixed DLB with AD, 19 PDD, 48 HC	Y	Differential aSyn pathological patterns in DLB, mixed DLB-AD, and PDD. ASyn distribution associated with motor impairment, visual hallucinations	3, 4

Table 1 (continued)

Citation	Sample characteristic	Pathology: y/*n*	Copathology studied / found	Type of evidence*
Liu et al. 2023 [120]	210 de novo-PD including 142 PD-NC and 68 PD-MCI	N	CSF GFAP predicts longitudinal changes of both aSyn and AD biomarker levels (p-tau181, t-tau, Aβ42)	2
Corticobasal syndrome / degeneration (CBS / CBD) and Progressive supranuclear palsy (PSP)				
VandeVrede et al. 2025 [44]	125 AD, 35 CBS, 40 PSP, 10 DLB, 16 HC, 118 FTD, 5 ALS	Y	AD copathology was found in 25% of PSP and 40% of DLB 40%	1, 2, 3, 6
Kurz et al. 2025 [121]	27 AD, 26 Aβ(-) CBS, 17 HC	N	Blood Aβ42/40, ptau181, ApoE4, GFAP, NfL. PET and CSF in AD-CBS	2
Forrest et al. 2019 [88]	126 FTLD	Y	2 PSP, 2 CBD, 2 PiD and 3 FTLD-TDP43 had LBD copathology. All FTLD-TDP43 with LBD copathology had progranulin or C9orf72 mutations.	2, 6
Videira et al. 2020 [119]	1 CBS	Y	Case report of a CBS patient with PSP, AD and LBD pathology	5, 6
Aiba et al. 2023 [74]	32 CBD	Y	The vast majority of CBD cases (26/29) had no or very little Aβ copathology (Thal phase ≤1)	
Coughlin et al. 2022 [125]	17 CBD, 57 AD, 40 PSP, 36 mixed DLB with AD	Y	After exclusion of AD cases with evident LBD, 29/57 of the AD cases still exhibited aSyn copathology in the amygdala	5
Ghirelli et al. 2020 [79]	10 CBD, 10 PSP, 3 FTLD-TDP43, 1 PiD	Y	Only 1/10 CBD and 2/10 PSP had moderate to severe Aβ copathology (Thal phase≥3, with CAA findings). 1 CBD and 2 PSP also had mild Aβ copathology.	1, 5
Kim et al. 2023 [126]	20 CBD, 30 AD, 10 globular glial tauopathy, 20 PiD, 20 PSP, 21 HC	Y	Aβ copathology was largely absent or mild in CBD and PSP	5
Lantero-Rodriguez et al. 2024 [127]	20 CBD, 20 HC, 20 AD, 11 PSP	Y	Aβ copathology was investigated in 10 CBD and found to be moderate to severe in 3 of them (Thal phase≥3, with CAA findings), and mild in 2	5
Ling et al. 2020 [83]	6 rapidly progressing CBD, 4 intermediate-stage CBD, 110 classic CBD	Y	AD pathological features and CAA were absent in 5/6 of the rapidly progressing CBD, suggesting no contribution of copathology to rapid progression. Same pattern was observed in the 110 classic CBD.	5
Maldonado-Diaz et al. 2024 [76]	6262 subjects with neuropathology: 121 CBD and 221 with PSP	Y	Presence of AD neuropathological features was negatively correlated with CBD	5
Mimuro & Iwasaki 2024 [78]	21 CBD	Y	2/21 showed moderate Aβ copathology (Thal phase≥3) and 10/21 had mild Aβ co-pathology	5
Pennington et al. 2020 [75]	515 pathologically confirmed FTLD including 82 CBD, 210 PSP, 53 PiD, 139 FTLD-TDP43	Y	In CBD and PSP, age was associated with higher likelihood of having changes on the AD spectrum. For CBD, 3.7% met criteria for a secondary diagnosis of AD, 15% had AD features, and 12% CAA. In PSP, only 2% met criteria for a secondary diagnosis of AD, 11% had AD features, and 5% CAA	5
Riku et al. 2022 [77]	12 CBD, 26 PSP, 21 AD, 6 PiD, 5 globular glial tauopathy, 36 CN	Y	Aβ copathology was largely absent to mild in the CBD (mean Thal phase: 0.4 ± 0.7) and PSP (mean Thal phase: 1.1 ± 1.5)	5
Samudra et al. 2024 [80]	3 CBD, 7 PSP	Y	AD copathology was absent to mild in all CBD and 6/7 PSP	1, 5
Shir et al. 2024 [128]	82 patients with primary progressive aphasia clinical syndromes, pathologically: CBD (12), PSP (9), AD (30), LBD (5)	Y	None of the CBD had AD copathology. 17% of the AD had LBD copathology snd 80% of LBD had AD copathology. Copathology in PSP was mainly AD	1, 5
Soleimani-Meigooni [129]	2 CBD, 4 PSP, 8 AD, 5 other FTLD, 1 AGD	Y	AD copathology found in one PSP and no CBD. 3/8 AD had LBD copathology	5
Hiya et al. 2025 [81]	4624 subjects with neuropathology: isolated AD (126), isolated cerebrovascular disease (76), PSP (61), CBD (23), PiD (22), isolated PART (18), isolated FTLD-TDP43 (18), isolated LATE-NC (14), isolated LBD (11), isolated AGD (4), isolated ALS (2), and mixed pathologies	Y	Out of 116 subjects with CBD features, 23 showed no co-pathology (isolated CBD), and 7 had moderate AD copathology. Out of 237 subjects with PSP features, 61 showed no copathology (isolated PSP). 7 CBD and 15 PSP had moderate AD copathology, but this did not significantly modify their phenotype, which remained overall similar to isolated CBD and PSP cases	1, 5

Table 1 (continued)

Citation	Sample characteristic	Pathology: y/*n*	Copathology studied / found	Type of evidence*
Wang et al. 2023 [130]	1 CBD, 2 AD, 7 PSP, 5 LBD, 7 mixed LBD with AD, 4 MSA, 1 minimal atrophy	Y	No PSP had AD copathology. The CBD case had intermediate AD neuropathological changes. Of all patients with either AD or LBD primary diagnosis, half presented with a mixed pathology (concomitant LBD and AD)	5
Yoshida et al. 2025 [131]	5 CBD, 26 HC, 31 AD, 16 LBD, 38 mixed LBD with AD, 14 MSA, 36 PSP	Y	AD copathology was largely absent or mild in the CBD, PSP, and MSA cases (mean AD neuropathological changes level: 0.8 ± 0.8, 0.9 ± 0.8, 0.4 ± 0.5 respectively). Mixed LBD with AD was more common than either pure AD or LBD, and showed distinct protein deposition patterns	5
Saijo et al. 2020 [132]	9 CBD, 8 PiD, 9 AD, 3 chronic traumatic encephalopathy, 4 LBD, 3 PART, 16 PSP, 11 FTLD due to MAPT mutation, 3 FTLD-TDP43, 3 MSA, 1 ALS, 12 other	Y	Only 1 PSP and no CBD had Aβ copathology (CAA)	5
Garcia-Cordero et al. 2022 [2]	87 AD(-) CBS/PSP, AD (+) CBS/PSP, 18 AD, 30 HC	Y: only 3	AD biomarker positive CBS and PSP patients showed atrophy in AD areas and the brainstem. There was greater default mode network disconnection in the AD (+) CBS and PSP, and reduced thalamic network connectivity in the AD (-) CBS/PSP	1, 6
Wang et al. 2024 [116]	46 AD, 5 CBD, 33 PSP, 43 NC, 6 PiD	Y	AD copathology found in 1/5 CBD, and LBD copathology in 4/33 PSP	6
Couto et al. 2022 [115]	4 PSP long disease duration	Y	4/10 PD and PDD cases had tau positive NFTs, including PART and AGD	1, 2, 6
Robinson et al. 2020 [82]	247 AD, 29 CBD, 51 PSP, 138 LBD, 26 MSA, 108 ALS, 80 FTLD-TDP43, 15 PiD, 72 minimal pathology	Y	Aβ co-pathology very frequent, and seen in 41%, 57%, 38%, and more than 50% of the CBD, PSP, MSA, and LBD cohorts respectively. In LBD, more advanced aSyn pathology with 80% Aβ co-pathology. In CBD, PSP, and MSA: mild Aβ and without clinical impact	5
Sakae et al. 2020 [80]	128 CBD	Y	41 had intermediate to high concomitant AD pathology (Braak NFT staging > III and Thal phase > 0).	5
Multiple system atrophy (MSA)				
Homma et al. 2020 [114]	14 MSA	Y	Tau-positive granular glial pathology in putamen and cerebral white matter	2, 6
Tanaka et al. 2024 [117]	2/3 cases: one parkinsonism with rapid cognitive decline, clinical MSA	Y	Nigral tau-astrogliopathy: high ARTAG, milder neuronal tau pathology in SN	1, 2, 6
Homma et al., 2022 [118]	3 atypical MSA	Y	MSA, tufted astrocyte-like glia, few or none of the other PSP criteria	6
Ando et al. 2021 [52]	1 MSA	Y	Clinical MSA with "hot-cross bun" sign in brain MRI with pathology of CBD	1, 3
Carlos et al. 2022 [53]	1 MSA	y	MRI, 18 F-deoxyglucose and Flortaucipir→ differentiate MSA from PSP	1, 6

Abbreviations: *Aβ* amyloid-beta, *AD* Alzheimer's disease, *ADNI* AD neuroimaging initiative, *AGD* argyrophilic grain disease, *ALS* amyotrophic lateral sclerosis, *ARTAG* aging-related tau astrogliopathy, *CAA* cerebral amyloid angiopathy, *CBD* corticobasal degeneration, *CBS* corticobasal syndrome, *DLB* dementia with Lewy bodies, *FTD* frontotemporal dementia, *FTLD* frontotemporal lobar degeneration, *FLD-TDP43* FTLD due to TAR DNA-binding protein 43, *GFAP* glial fibrillary acid protein, *HC* healthy controls, *iRBD* idiopathic/isolated (Rapid Eye Movement)-sleep behavioral disorder, *LATE-NC* limbic-predominant age-related TDP-43 encephalopathy, *LBD* Lewy body disease, *MCI* mild cognitive impairment, *NC* normal cognition, *NfL* neurofilament light chain, *NFTs* neurofibrillary tangles, *PART* primary age-related tauopathy, *PD-CI* Parkinson's disease with cognitive impairment, *PDD* Parkinson's disease dementia, *PET* positron-emission tomography, *PSP* progressive supranuclear palsy, *P-tau181* phosphorylated tau at threonine 181, *P-tau231* phosphorylated tau at threonine 231, T-tau total tau, *VascD* vascular dementia

*Types of evidence: 1- imaging biomarker; 2- biofluid or biosample (eg: skin) biomarker; 3- Aß in PD; 4- Tau in PD; 5- Aß in AP; 6- Tau in AP

6,262 patients with neurodegenerative diseases (121 with CBD). In smaller cohorts, co-pathology prevalence varied between 10 and 30% [78–80]. Differences in the definition of co-pathology may contribute to some variability in the literature. For instance, while Sakae et al. reported one third of 128 CBD cases met their criteria for concomitant AD (defined as Braak stage > III and Thal > 0), metrics of amyloid spread were very low (median Thal phase, 25–75% percentile: 0, 0–1) [80].

A few studies have explicitly assessed antemortem biomarkers against post-mortem findings of Aß co-pathology – as expected, only cases with significant co-pathology (i.e. frequent diffuse plaques) could be detected using antemortem amyloid PET [79]. Considering how rarely severe Aß co-pathology appears to be in CBD, this suggests that AD is the primary neuropathological diagnosis in most AD biomarker-positive CBS subjects. In regards to clinical presentation, while a recent study has reported an association between the presence of Aß co-pathology and symptoms-type and severity in CBD [81], further research is needed to disentangle the effect of co-pathology itself from other confounders, particularly age-related factors. Indeed, Aß co-pathology in CBD has been found to be age-related in several studies [73, 76, 77]. Generally, there is little evidence that Aß co-pathology modifies clinical presentation in the context of CBD [82], nor is it involved with faster progression and clinical milestone latency [83].

For PSP, reports have shown a varied prevalence of co-pathology [70], ranging from 6% to 57% [84]. A recent analysis of the National Alzheimer's Coordinating Center (NACC) of the U.S. dataset found 69% of PSP-pathology confirmed cases with different concomitant pathologies: 76% arteriolosclerosis, 30% ADNC, 8% LBD, 4% CBD, 36% CAA, and 33% lacunar infarcts [85]. A similar report found ADNC in 24% of PSP (15/61 cases [81]. As in CBD, clinical severity, particularly of cognitive-behavioral impairment, were mostly dependent on PSP pathology and only increased in cases with ADNC-co-pathology [77, 83] maintaining the same profile seen in cases with pure PSP [84].

Tau Co-pathology in AP Disorders

The most recent evidence of tau co-pathology in LBD and MSA includes large cohorts and reports from brain banks. Given that tau is a major feature of the 4R-tauopathies PSP and CBD, we summarize in the Table the reports of patients harboring those diagnoses with atypical or additional neuropathological changes of tau such as ageing-related tau astrogliopathy (ARTAG), and nigral ARTAG (NITAG).

As mentioned above, the neuropathology of DLB associates with ADNC in up to 80% of cases [70]. Cross-sectional data analysis of the BIOFINDER2 cohort recently reported by Pichet Binnette et al. [54] found 83 patients with moderate tau staging (assessed by tau-PET imaging pattern) who had discordant severe clinical staging. Of those, 27 cases had LBD, all of them had a Aß-positive PET-scan and post-mortem confirmed ADNC co-pathology. Those discordant cases were older, of higher male proportion, had less formal education, and were more likely to have had cardiovascular or cerebrovascular ischemic disease than not-discordant cases. In the same cohort, 35 DLB/PDD previously reported cases by Hall et al. [33], with abnormal tau-PET were found to have higher levels of plasma and CSF p-tau217 and p-tau181. Additionally, p-tau correlated negatively with $Aß_{42}/Aß_{40}$ ratio suggesting that plasma p-tau can accurately predict ADNC co-pathology in LBD with the limitation that those patients lacked neuropathology confirmation. A more recent study in the Massachusetts AD Research Center's cohort on PD and LBD cases, up to 54% cases had ADNC, particularly 9/21 of LBD showed co-pathology [34]. In this cohort, p-tau181 levels correlated with LBD-ADNC-positive scores in the cortex (any of Braak stage, Thal phase, and CERAD neuritic plaque). The association of tau and ADNC with symptoms and syndromic presentation in cases of LBD has shown controversial. In a different PDD/DLB cohort from Philadelphia, 30 neuropathologically confirmed cases were found to have evidence of ADNC by CSF biomarkers which manifested in life with higher clinical scores of axial and non-tremor motor impairments such as postural instability-gait dysfunction [PIGD, 39].

Neuropathology studies have typically reported very low presence (7-14.5%) of co-pathologies in MSA cases [86, 87] mostly with low Braak-stage. A study looking at brain bank series of FTLD cases found only 9/126 showed LBD (2 PSP, 2 CBD, and 2 Parkinsonism with dementia) but none had pathology of MSA [88]. This lack of MSA co-pathology with tau proteinopathy has been recently challenged by Kon et al. who reported 4/21 cases of MSA with pathological Aß deposits in the striatum and cerebellum as well as moderate stage tau pathology (beyond PART), with different α-synuclein-SAA kinetics but similar clinical, radiological and pathological stage [89]. The same group in Toronto reported tau-positive SAA test in 1/18 patients with clinical MSA, and none with pathologically confirmed MSA [19, 90–93].

Discussion

Summarizing the reviewed evidence, in PD and DLB, Aß fluid biomarkers may be useful predict clinical trajectory and cognitive decline highlighting a prognostic value, while PiB-PET would help stratifying patients and directing

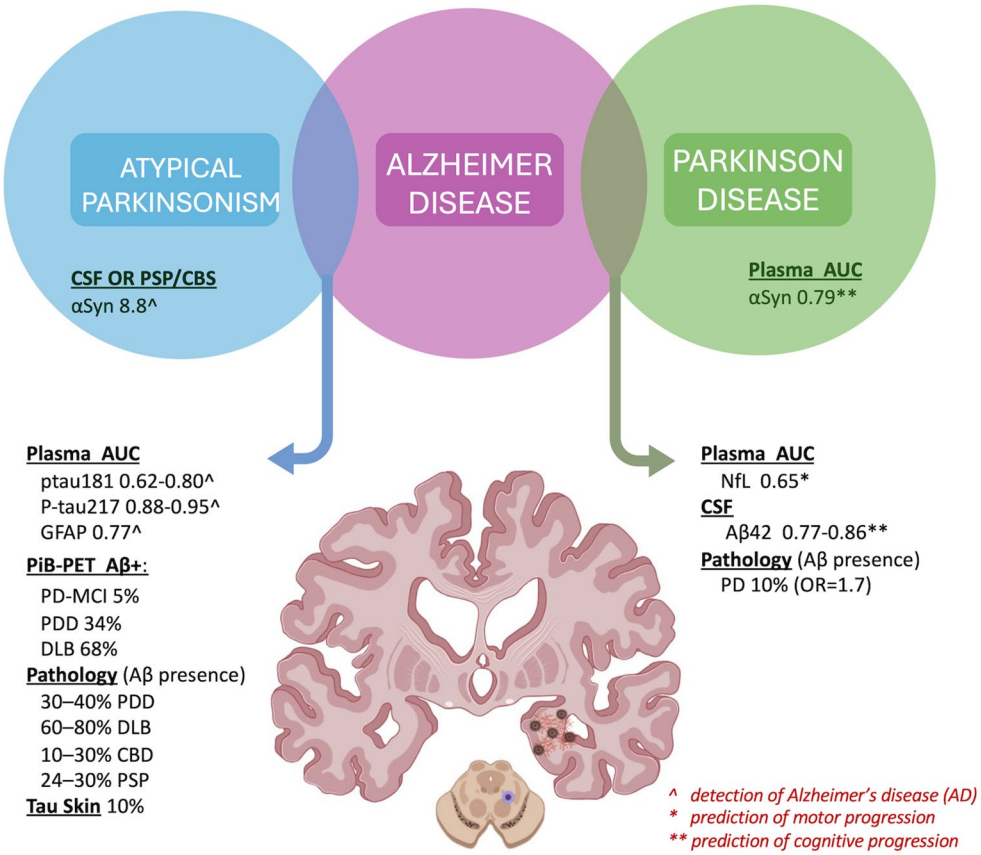

Fig. 1 Visual summary of the most relevant biomarkers and neuropathology. Abbreviations: AUC, Area Under the Curve. CSF: cerebrospinal fluid GFAP, glial fibrillary acid protein; NfL, neurofilament light chain;PSP, progressive supranuclear palsy; PD, Parkinson disease; PDD, Parkinson's Disease Dementia

therapeutic pipeline designs. The reason why not tau biomarkers and Aß only partially correlates with clinical progression in PD/DLB highlights the need for harmonization of methodological procedures. Different population selection criteria, as well as the recency and novelty of plasma tau biomarkers render the reviewed studies with confounders for the interpretation of their results. In three of the AP disorders (PSP, CBD and MSA), although plasma ptau might not yet be of value, a combined multimodal assessment of PET imaging, MRI and fMRI with fluid biomarkers shall guarantee future differential diagnosis and prediction of clinical outcomes (Figure 1). The ongoing initiatives for validating SAA-based biomarkers to estimate co-pathologies might help clarify the interpretation of multimodal imaging and fluid biomarkers if replicated in different but deep-phenotyped cohorts of AP [94–98].

Pathophysiological Relation Between Tau, α-Synuclein, and Aß

In physiological conditions the interplay between tau and αSyn is crucial for neuronal development and microtubule stability. In pathological contexts αSyn and tau are prone to misfolding and can interact synergistically, contributing to neurodegeneration through co-aggregation an cross-seeding mechanisms [99]. Cross-seeding has been demonstrated in animal models, where pathological αSyn or tau can induce aggregation of the other protein. Clinical evidence shows that both proteins can propagate in a prion-like manner affecting neurons previously containing no pathological aggregates as seen in PD patients with grafted neurons [100–102]. Mutations in *SNCA* or *MAPT* genes accelerate the transition from soluble forms to insoluble aggregates as demonstrated by the familial-PD A53T mutation: tau mediates postsynaptic dysfunction, A53T-αSyn can drive GSK3β- mediated tau phosphorylation leading to tau mis-localization to dendritic spines and to calcineurin/AMPA-mediated impairment of postsynaptic activity. These mechanisms contributed to the cognitive deficits observed in familial A53T-PD [103].

The relationship between tau and αSyn occurs at different cellular levels, mitochondrial dysfunction and oxidative stress are central to PD pathology, with αSyn and tau playing significant roles in neurodegeneration [104]. Experimental models feed-forward interaction among Aβ, tau and α-synuclein. Aβ fibrils catalyze tau phosphorylation and aggregation, whereas soluble Aβ oligomers enhance αSyn seeding and disrupt proteostasis [105]. Findings in patient samples align with that: Lewy body disease patients with high Aβ load display distinct cortical proteomic signatures enriched for synaptic and mitochondrial stress pathways [106]; and SAA studies detected faster αSyn seeding kinetics in Aβ-rich brains [89]. The net effect would be an

accelerated dysfunction at the network level leading to earlier and more pervasive dementia.

Considerations from Neuropathology and Its Recent Biological Definitions of Neurodegenerative Diseases

Weather tau pathology shall be an upstream driver of and precede Lewy pathology in nigrostriatal degeneration [69] and Lewy pathology may emerge later or act as a secondary contributor in Parkinson's disease is a matter of recent debate. As we have reviewed it here, co-pathology is more the rule than an exception in most neurodegenerative disorders. Although most of the published research on SAA-based biomarkers claim a high degree of sensitivity, a negative assay can be found in a significant proportion of cases, thus making these tests not universally applicable yet [107]. The same holds true for specificity, as αSyn-SAA positivity has been shown to occur in PSP and CBD as well as in AD [108–111]. As it has been argued within the AD biomarkers field, a purely biological definition risks a category error at the same time that emphasizes the need for longitudinal data to establish the lifetime risk of dementia in Aβ-positive and tau-positive individuals [112]. At this point, the possibility of establishing a differential diagnosis with a high degree of certainty between different synucleinopathies or tauopathies with the newest SAAs remains to be demonstrated. We consider that the evidence of co-pathologies reviewed here would call to caution regarding the use a pathological biomarker as an indication of the biological processes underlying neurodegeneration.

Conclusion

This literature review shows that the co-pathology is frequent and clinically relevant in PD and AP, more relevant related to age, contributes to clinical heterogeneity, influencing cognitive decline, motor progression, and biomarker trajectories. In this era, fluid and imaging biomarkers especially Aβ42, p-tau, NfL, GFAP offer valuable insights into underlying pathology and disease progression, although current thresholds may require adaptation for PD and AP populations. in AP (DLB/CBS), plasma p-tau217 and p-tau181 are promising as reliable indicators of ADNC. Neuroimaging findings, as cortical thinning and hypometabolic patterns, reflect the burden of co-pathologies. Despite advances in SAA and multimodal biomarker strategies, the distinction between primary and secondary pathologies remains challenging without neuropathological confirmation. In conclusion, comprehensive biomarker profiling has the potential to refine diagnostic accuracy, improve patient stratification and guide therapeutic development in these coexistence neurodegenerative syndromes. Future longitudinal and autopsy-confirmed studies are warranted to establish the prognostic utility and clinical applicability of biomarker-based co-pathology detection.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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