REVIEW

Pathological Influences on Clinical Heterogeneity in Lewy Body Diseases

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ABSTRACT: PD, PD with dementia, and dementia with Lewy bodies are clinical syndromes characterized by the neuropathological accumulation of alpha-synuclein in the CNS that represent a clinicopathological spectrum known as Lewy body disorders. These clinical entities have marked heterogeneity of motor and nonmotor symptoms with highly variable disease progression. The biological basis for this clinical heterogeneity remains poorly understood. Previous attempts to subtype patients within the spectrum of Lewy body disorders have centered on clinical features, but converging evidence from studies of neuropathology and ante mortem biomarkers, including CSF, neuroimaging, and genetic studies, suggest that Alzheimer's disease beta-amyloid and tau copathology strongly influence clinical heterogeneity and prognosis in Lewy body disorders. Here, we review previous clinical biomarker and autopsy studies of Lewy body disorders and propose that Alzheimer's disease copathology is one of several likely pathological contributors to clinical heterogeneity of Lewy body disorders, and that such pathology can be assessed in vivo. Future work integrating harmonized assessments and genetics in PD, PD with dementia, and dementia with Lewy bodies patients followed to autopsy will be critical to further refine the classification of Lewy body disorders into biologically distinct endophenotypes. This approach will help facilitate clinical trial design for both symptomatic and disease-modifying therapies to target more homogenous subsets of Lewy body disorders patients with similar prognosis and underlying biology.

Key Words: Parkinson's disease; dementia with Lewy bodies; alpha synuclein; neuropathology; clinical heterogeneity

Parkinson's disease (PD) is a common neurological disorder, affecting over 10 million people worldwide,[1] and is marked by highly variable extrapyramidal motor features of tremor, rigidity, and bradykinesia, but also nonmotor features of depression, autonomic dysfunction, and cognitive impairment. The reasons for this heterogeneity are unknown. Cognitive impairment and dementia are particularly strong predictors of poor prognosis.[2] Cognitive impairment is present in approximately 25% of patients in early stages of the disease and predicts faster progression to dementia,[3,4] which is likely inevitable but occurs at widely variable times after the onset of motor parkinsonism.[5,6] Early efforts to create clinical subgroups were based on the observation in large cohort studies and clinical trials that disease progression was more benign in some patients with a particular set of motor symptoms than in others. Subsequent work has integrated new genetic markers, imaging characteristics, and cerebrospinal fluid (CSF) analytes in both hypothesis-driven studies and data-driven cluster analyses. However, robust, reproducible, clinical subgroups have been difficult to identify.

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The diagnostic neuropathologic hallmark of PD is misfolded alpha-synuclein (SYN) aggregates that form intraneuronal Lewy bodies (LB) and Lewy neurites (LN; collectively, Lewy pathology [LP]). The introduction of immunohistochemical staining for SYN increased the sensitivity to detect these aggregates in PD and also revealed SYN accumulations in the neocortex of many patients previously diagnosed with Alzheimer's disease (AD).[7,8] The neuropathological terms to describe this mixed pathology varied in early literature, but many of these patients showed clinical features distinct from amnestic AD. The clinicopathological syndrome of dementia with Lewy bodies (DLB)[9-11] was defined by consensus criteria in 1996, with core features of motor parkinsonism, visual hallucinations, fluctuations of alertness, and dementia. Criteria have been subsequently revised to include biomarkers to improve the sensitivity of clinical diagnosis.[12,13] Historically, the onset of the dementia should either predate or occur within 1 year of the onset of the motor parkinsonism, the so-called 1-year rule, in order for a diagnosis of DLB to be considered. However, because the clinical features of DLB and PD with dementia (PDD) are similar[13,14] and the two entities share genetic risk factors,[15-17] prodromal features,[18-20] and exhibit similar neuropathological features at autopsy,[9,21-23] the concept of a distinct separation between these overlapping conditions has been challenged by many investigators, who regard PD, PDD, and DLB as a single disease, LBD, whose clinical features are spread across a spectrum.[9,23,24]

Whereas SYN is the hallmark pathology of LBD, tau and beta-amyloid (Aβ) copathology is common (overall ~50% of all LBD have a secondary neuropathological diagnosis of medium- or high-level AD in most large autopsy series; see below).[21,24-28] Several converging lines of evidence indicate that AD copathology not only contributes to decreased survival and a shortened motor-dementia interval, but also influences specific motor and cognitive features.[21,25,29-32] Whereas in vivo SYN biomarkers are still being developed, methods to detect Aβ and tau in living LBD patients are improving.[33-37] Here, we will review previous and ongoing efforts to connect LBD patient subtypes with ante mortem biomarkers and underlying neuropathology to improve understanding of the biological basis of LBD's clinical heterogeneity.

The Role of Alpha-Synuclein in LBD Pathogenesis

In 1997, a mutation in the *SNCA* gene coding for SYN was discovered in a Greek/Italian family with autosomal dominantly inherited PD. Later that year, SYN was reported to be the major constituent of LB and LN found in both PD and DLB.[7,38] Landmark work by Braak and colleagues in 2003 proposed a conserved pattern of spread of LP in the brains of patients with PD, starting in the caudal brainstem and progressing rostrally through the upper brainstem, limbic regions, and finally the neocortex.[39] Other staging systems have emerged,[12,40] and additional patterns of LP have been added to account for the frequent finding of LP in the amygdala and limbic regions of patients with AD.[41-43] Current hypotheses regarding why particular regions of the brain are affected selectively include the spread of pathology along functionally connected networks[44] and selective vulnerability of long unmyelinated axons.[45] LP in DLB is thought to ascend the neuroaxis in a similar caudorostral pattern,[12,46] although the prominence of early dementia with limited or no motor parkinsonism—rare patients without dopamine transporter deficits on single-photon emission computed tomography imaging[47] and rare autopsy cases with isolated neocortical SYN pathology without brainstem or limbic SYN[48]—suggests an alternative pattern of spread in some cases.

The observations of SYN Lewy-like pathology in transplanted mesencephalic grafts in PD patients[49] support a "prion-like" mechanism of spread of misfolded SYN aggregates as central to disease pathogenesis. Moreover, recent experiments in cell and animal models use preformed SYN fibrils[50,51] or brain homogenates from human LBD subjects[52,53] to induce spread of SYN pathology that results in neuron loss and dysfunction as well as motor phenotypes which further supports this theory. Most recently, separate SYN species have been identified that may have different "strain-like" properties, with certain preparations being additionally capable of cross-seeding either tau[54-56] or Aβ[57] and others leading to MSA-type pathologies.[58-60] However, the core prion feature of infectivity has not clearly been demonstrated for LBD or AD in humans.[61]

Many autopsy studies have shown a correlation of LP with motor disease severity in PD.[43,62] The majority of studies have found that PDD is associated with either limbic (transitional)[13] or neocortical (diffuse) stage LB pathology[63-67] with higher cortical LP density being observed than in nondemented PD.[2,64-70] Neocortical LP is also associated with the onset of visual hallucinations,[70] and hippocampal SYN pathology is associated with memory deficits even after controlling for age and co-occurring pathologies.[71] The current neuropathological assessment of DLB recognizes that cases with pure synucleinopathy without AD copathology are the most likely to exhibit core DLB features or visual hallucinations and fluctuations.[13] Although LP is observed often at autopsy in asymptomatic individuals (incidental Lewy body disease; ILBD),[29,72,73] it is frequently less severe than the SYN pathology observed in DLB and PD[74,75] and is associated with mild degrees of nigral neuron loss and tyrosine hydroxylase–positive neuron loss, suggesting that ILBD may be a preclinical state before motor symptoms of an LBD emerge.[75-78] Some studies have not observed strong correlations between LP and neuronal loss in the SN[75,79] or other brain regions.[26] These data could suggest that LP is an epiphenomenon rather than central to disease pathogenesis[80]; however, there are several alternative explanations. It is suggested that oligomeric SYN species, which predate LB formation, may be more toxic than more mature species[81,82] and may therefore result in cell death apart from visible LP post mortem. Synaptic dysfunction from these early SYN species may lead to neuronal dysfunction rather than frank cell death.[83,84] Furthermore, as opposed to the extracellular pathology of tau neurofibrillary ghost tangles left behind from degenerated neurons, LP is cleared after cell death, leaving minimal "ghost" pathology detectable in highly degenerated regions.[85] Last, different methods and different antibodies used to detect SYN inclusions may show different degrees of pathology.[86,87] Although SYN pathology is diagnostic for LBD, further understanding of the biological mechanisms of SYN aggregation and associated neurodegeneration are needed, and it is possible that cell-autonomous factors may also influence the spread of pathogenic SYN to selectively vulnerable neurons with resultant neurodegeneration.[88]

AD Neuropathology

Aβ plaques and tau-positive neurofibrillary tangle pathology sufficient for a secondary neuropathological diagnosis of AD occurs in ~10% of PD, ~35% of PDD, and ~70% of DLB patients (overall ~50% of all LBD).[21,24-28] In some studies, higher degrees of Aβ plaques have been identified in neocortical, limbic, and striatal region in DLB than PDD,[89,90] and striatal Aβ plaques have also been shown to be more severe in PDD than nondemented PD patients.[91] Although these group-wise differences exist between PDD and DLB, there are no neuropathological findings that reliably distinguish these clinical phenotypes on an individual patient level.[21,22] Tau neurofibrillary tangle pathology is most often shown to have a similar distribution as observed in typical AD using conventional neuropathological staging methods,[92] but more recent digital assessments suggest relative sparing of medial temporal lobe[93] and greater relative distribution in temporal neocortex in LBD versus AD.[94]

Several investigations of the neuropathology of LBD have shown that coexistent AD pathology may influence the onset of dementia in PD.[21,25,65,66,69,95,96] In patients with PDD, AD copathology is associated with older age, decreased motor-dementia interval, and decreased overall survival.[21,25,29,97,98] Two of these studies reported that tau and Aβ pathology had a greater impact on the age of dementia onset than SYN alone.[32,96] Studies differ on whether tau[21] or Aβ[99] is the most significant contributor to dementia and shortened survival.[100] AD copathology has also been associated with a greater burden of neocortical deposition of SYN.[21,65,69,94,96,99,101,102] These disparate conclusions may be, in part, attributed to the high correlation between these pathologies[21,94] and relatively sparse sampling and qualitative ratings used on traditional autopsy studies.

Co-occurring tau and Aβ pathology may affect specific clinical features in LBD as well overall prognosis. In DLB, several studies have reported that increasing levels of tau and Aβ are associated with a decreased likelihood of visual hallucinations or attentional fluctuations.[30,31,103] These observations have resulted in alterations to the neuropathological assessment of DLB, whereby higher stages of tau are associated with a lower likelihood of patients exhibiting a "classic" DLB phenotype.[13] Other studies have documented alterations in domain-specific cognitive function in LBD patients with co-occurring tau and Aβ pathology at autopsy.[94,104,105] In PD, patients with tau and Aβ copathology are more likely to have a clinical phenotype of postural instability with little or no tremor (the "postural-instability-gait dysfunction" or PIGD phenotype).[25,32,106] Whereas co-occurring tau and Aβ pathology is often associated with worse prognosis in LBD, several studies also describe small groups of patients with "pure" synucleinopathy at autopsy with a fulminant course suggesting other potential biological sources of clinical heterogeneity.[95,103,107]

The studies listed above have relied on traditional neuropathological assessments which use semiquantitative, subjective ordinal measurements and severity scales that tend to emphasize topography rather than density of pathology.[12,108] Digital histological measurements, using image analysis techniques, offer a potential improvement over traditional methods by generating objective, finely grained, continuous measurements of pathological burden, which, in contrast to the traditional methodology, may improve the potential to make clinicopathological correlations and relate pathological burden to ante mortem biomarker assessments. However, more work is needed to standardize methodology across labs.[93,94,100,109] In our recent work using digital histology, we found that co-occurring tau and Aβ pathology was related to a higher burden of neocortical SYN in patients with LBD. The degree of tau pathology was several fold less in LBD compared to age-matched AD patients even when comparing subjects with similar Braak tau stages. We also found that tau in LBD occurred in a different distribution than in AD, with more relative temporal neocortical pathology. Last, we also found that regional tau burden was consistently related to worse cognitive performance both on measures of global cognition and domain-specific testing.[94] Another recent digital study of LBD found relative sparing of tau pathology in the hippocampus of LBD patients with AD copathology, compared to patients with clinical AD and mixed AD and SYN pathology.[93] Finally, others find similar correlation of mixed SYN, Tau, and Aβ pathology, with strong influence of neocortical SYN on overall survival in DLB.[100] Together, these studies highlight the ability of digital methods to enhance clinicopathological correlations and suggest that the distribution of tau in LBD may diverge from AD and influence clinical phenotype.

Subtyping by Clinical Features

Tremor-Dominant Versus Postural Instability Gait Disorder

Early attempts to parse the clinical heterogeneity of PD centered on two motor subtypes: (1) predominant rest tremor (tremor dominant; TD) with relatively less bradykinesia, rigidity, and postural instability and a slower rate of progression compared with (2) PIGD with significant gait and postural dysfunction and associated with older age of onset, more rapid progression and early onset of cognitive impairment.[110-115] The notion of motor-based subtypes was first promoted in H & Y's 1967 description of the clinical features of PD[116] and has been recapitulated in other publications since.[117,118] Commonly used motor scales may be used to assign designations.[110,119,120] Nonmotor symptoms, such as depression and autonomic dysfunction,[121,122] have been reported with greater frequency and severity in PIGD patients than in TD patients.[123,124] In addition, patients with a higher burden of PIGD signs have decreased survival when matched to other patients with similar age and disease duration.[125,126] Patients with lower CSF Aβ and higher CSF tau (i.e., findings indicative of underlying AD copathology) are more likely to have a PIGD phenotype.[127,128] One of these studies was a partial analysis of PD patients with new-onset disease recruited to the PPMI (Parkinson Progression Markers Initiative), a project sponsored by the Michael J. Fox Foundation, but a subsequent analysis failed to reproduce the earlier result.[34] Amyloid PET imaging has shown a greater likelihood of increased cortical tracer retention in PIGD versus TD.[129] There are minimal data directly comparing motor symptoms of DLB patients with and without co-occurring AD pathology, but the majority of reported autopsy cases suggest less prominent rest tremor or a greater likelihood of PIGD phenotypes in DLB than PD,[112,130] which aligns with the knowledge that DLB overall is more likely to harbor coexisting AD pathology than nondemented PD cases.

There are problems with TD and PIGD distinctions. Many patients in large cohorts have clinical features of both phenotypes and therefore fall into an "intermediate" category of uncertain significance,[124,131] and many patients will change designations, typically from TD to PIGD, over the course of their illness.[112,131,132] The designations are particularly unstable early in the disease course.[131]

Age of Onset

Age of onset is also a well-recognized predictor of progression. The Sydney Multi-Center Study followed 136 patients from onset of PD symptoms over the course of 20 years and has shown that a younger age of onset was associated with a longer course and also that an older age of onset was associated with decreased survival and greater likelihood of tau and Aβ copathology.[5,95] These observations are not surprising, given that age is a risk factor for AD pathology, even in asymptomatic elderly individuals. Most subsequent studies have found that an older age of onset is associated with a greater burden of motor disease at diagnosis with a faster decline in motor scores, shorter motor-dementia interval, and a greater burden of PIGD scores.[110,133-137] It is notable that the prognostic value of age of onset appears to be independent from disease duration[137] and from postmortem severity of AD pathology.[21]

Data-Driven Patient Subtypes using Cluster Analyses

More recently, many have used a group of statistical data-driven methods known as cluster analyses to elucidate potential subtypes in different LBD populations. This type of approach is attractive given the data-driven approach rather than hypothesis-driven analyses. It is important to note that the clustering solutions and patient subtypes derived from these studies are, by definition, found in the specific population studied and are not always generalizable to other populations. Furthermore, the clustering solutions are derived from the variables that are collected a particular study. A review of the literature published after the year 2000, using PubMed and Medline using search terms "cluster analysis," "Parkinson's disease," and "Dementia with Lewy Bodies," yielded 11 studies: 10 in PD and one in DLB.[135,138-147]

Many of the above studies have recapitulated an older age and rapid progression phenotype[135,138,143,144,146,148] and some have shown groups with benign courses and tremor-predominant phenotypes similar to previous studies.[138,146] Others have found that groups with more PIGD-like phenotype are also marked by more severe motor deficits at onset, more nonmotor symptoms, and higher mortality.[125,139,140,142] In studies where such variables were included, nonmotor symptoms often proved to be stronger determinants of cluster membership than motor features.[139,141] Many of these studies have not attempted validation in other cohorts, and when it has been attempted, results have been disappointing.[140,141,145,146] One of the above cluster analysis studies incorporated CSF tau and Aβ levels into a post-hoc analysis and found that patients with the "diffuse-malignant" phenotype who had worse motor scores, higher PIGD subscores, higher autonomic dysfunction, worse cognition, and faster disease progression had lower CSF Aβ and higher tau than the other subtypes.[141] The details of the methods and results of these studies are detailed in Table 1. These purely clinical studies have not had pathological validation, except one recent publication which performed a retrospective cluster analysis and found no difference in SYN or co-occurring tau and beta Aβ pathology among their subgroups.[149]

In Vivo Biomarker Associations with Patient Subtypes

CSF

Cross-sectional studies of CSF Aβ1-42, total tau and 181 phospho-tau in LBD show wide ranges of values, with some patients having overlapping with healthy controls to others displaying pathological levels similar to AD.[24,150] In PD, most large studies find that CSF Aβ1-42 is lower than controls at diagnosis and is associated with worse memory impairment in more advanced disease.[4,151-158] Low levels of CSF Aβ1-42 have also been linked to faster motor progression.[156] In DLB, AD-like CSF values are more likely than in PDD[159] and lower Aβ1-42 and higher tau levels were associated with a greater likelihood of admission to a long-term care facility and higher mortality.[160] Total tau and 181 phospho-tau are reported to be either equivalent or lower than healthy controls in nondemented PD patients,[34,128,151,152] but higher in PDD.[153,161,162] An analysis of the DATATOP (Deprenyl And Tocopherol Antioxidant Therapy of Parkinson's) trial found that higher levels of CSF tau may be related to faster motor progression.[163] Whereas postmortem validation studies in LBD are rare, CSF measurements of tau and Aβ1-42 relate to the severity of AD pathology in LBD,[35,164] as previously observed in AD.[165-167] Interestingly, low CSF Aβ1-42 may also relate to neocortical distribution of SYN pathology.[35] Further work is needed to elucidate the relationship between ante mortem AD CSF biomarkers and underlying neuropathology and to continue to collect longitudinal data on CSF measurements in well-characterized cohorts.[168] Nevertheless, CSF tau and Aβ biomarkers appear to have some prognostic value in LBD, but further data are needed to clarify this association and longitudinal progression of these markers over time.[163,169]

In vivo SYN detection remains a critical need to advance LBD research. Developing a reliable assay for CSF SYN assay has proven difficult, in part because CSF SYN is present in relatively low amounts and leakage of peripheral blood into CSF during lumbar puncture can contaminate measurements.[170] Most, but not all, studies have found CSF total SYN to be lower in PD compared to healthy controls.[128,157,171-174] Higher levels of CSF total SYN were associated with faster cognitive decline in the DATATOP study.[156,175] A separate study reported lower levels of CSF SYN in patients with nontremor phenotypes.[34] Assays for phosphorylated and oligomeric CSF SYN, both likely more specific for pathological SYN, have shown elevations in patients with PD in some studies, but replication between centers has proven difficult.[153,175-178] Moreover, in AD, there are elevated levels of SYN that may represent leakage from damaged synapses, suggesting that underlying mixed AD copathology could alter total SYN levels in LBD.[150] More recently, real-time quaking induced conversion methods, which take CSF samples containing pathogenic SYN and incubate them in substrate containing nonaggregated SYN monomers and allow templating to happen in repeated cycles, allow for signal amplification of CSF SYN that may aid in demonstrating increases in PD and DLB patients over healthy controls.[179,180] Two drawbacks to this technique are the occasional false negatives and the fact that it is largely a binary measure given that detection is only currently possible after several amplification cycles.[180,181] Nonetheless, this is an emerging approach that utilizes the pathological aggregation of SYN from patient samples that may be beneficial to detect the presence of underlying synucleinopathy in vivo. The interaction of CSF SYN, tau, and Aβ in LBD continues to be investigated, but dynamic changes over the course of the disease are expected.

PET

Amyloid PET imaging studies show a gradient in the proportions of cases with increased retention across the LBD spectrum with generally low retention observed in PD to higher uptake in PDD and DLB.[24,182-186] ^{11}C-Pittsburgh compound B may be more specific for neuritic amyloid plaques, rather than diffuse plaques, and has been described to have greater neocortical retention in DLB than PDD.[187] The degree of amyloid tracer retention in patients with LBD is generally less than what is observed in AD.[188,189] Some studies have demonstrated that amyloid PET positivity is related to the presence and severity of cognitive deficits in PD[184,186,190,191]; however, this finding is not universal.[192] Several tau tracers have been developed, including ^{18}F- flortaucipir (formerly AV1451), ^{18}F-THK523, ^{18}F-5105, ^{18}F-FDDNP, and ^{11}C-PBB3,[193] some of which have been studied in LBD.[37,194,195] ^{18}F-flortaucipir uptake is elevated in some LBD patients compared to controls, often in patients who also have evidence of amyloidosis on PET imaging, and the degree of uptake is typically less than what is observed in AD.[37,194,195] Similar to rates of co-occurring tau and Aβ neuropathology, patients with a DLB phenotype are more likely to have elevated ^{18}F-flortaucipir uptake than nondemented PD.[195,196] Patterns of uptake in LBD have differed from AD by concentrating in posterior temporo-parieto-

TABLE 1. Cluster Studies in LBD

	Gasparoli et al., 2002 [134]	Dujardin et al., 2004 [141]	Lewis et al., 2005 [137]	Schrag et al., 2006 [142]	Post et al., 2008 [143]	Reijnders et al., 2009 [145]	Van Rooden et al., 2011 [144]	Fereshtehnejad et al., 2015 [140]	Erro et al., 2016 [138]	Fereshtehnejad et al., 2017 [148]	Morenas-Rodriguez et al., 2018 [146]
Design and Inclusion											
Patients, n	103	44	120	124	131	346	344	113	398	421	81
Inclusion	PD Dx <5y	PD Dx <3y	PD HY I-III	None	De Novo PD	None	PROPARK[a]	None	PPMI	PPMI	Probable DLB[b]
Age, mean years (SD)	NS	66 (median)	64.4 (9.3)	71.9 (11.0)	66.7 (10.4)	70.4[c]	60.8 (11.3)	66.7 (8.9)	63.2[c]	61.1 (9.7)	59.3 (48)
Disease Duration, mean years (SD)	NS	4 (median)	7.8 (5.4)	6.1 (4.4)	1.7 (0.9)	8.2	9.9 (6.2)	5.7 (4.2)	NS	0.5 (0.5)	5.0 (3.2)
Clustering Algorithm Type	NS	K-Means	K-means	K-Means	K-Means	K-Means	Model Based	K-means and agglomerative hierarchical	K-means	Agglomerative hierarchical	K-means
Variables Included in Clustering Solution											
Demographics											
Age of Onset			■	■	■	■			■	■	
Sex									■		
Motor Features											
UPDRSII	■							■	■	■	■ Motor Parkinsonism[d]
UPDRS III	■	■						■		■	■ Motor Parkinsonism[d]
Rate of Motor Progression		■	■	■	■	■					
Motor Phenotype			■	■	■	■	■		■	■	
Motor Complications (fluctuations, dyskinesias)	■			■		■	■				
Non-Motor Features											
Depression			■		■	■	■	■		■	
Anxiety					■			■	■	■	
Apathy						■			■	■	
Autonomic Dysfunction							■	■	■	■	
RBD								■	■	■	
Cognition		■	■	■	■	■	■	■	■	■	■
Hallucinations											■
Clustering Solutions											
N	2	2	4	2	3	4	4	3	3	3	3
Characteristics	Older age/ rapid progression (39%) Younger age/slower progression (61%)	Worse motor and cognitive impairment (36%) Milder motor and preserved cognition (59%)	Young onset (41%) Tremor dominant (17%) Non-tremor dominant (26%) Rapid motor progression (17%)	Young onset more depression (36%) Older onset more rapid progression (64%)	Young onset (34%) Intermediate age onset (27%) Oldest age onset, more rapid motor progression (40%)	Young Onset (29%) Tremor dominant (47%) Non tremor predominant with psychopathology (17%) Rapid disease progression (6%)	Young mild (49%) Youngest with motor and non-motor complications (13%) Older and intermediately affected (30%) Diffuse and severely affected (8%)	Mainly motor (38%) Intermediate (27%) Diffuse malignant (35%)	Mild motor/slow progression (45%) Worse motor (38%) Worse motor and non-motor burden (17%)	Mild motor predominant (52%) Intermediate (38%). Diffuse malignant (9%)	Cognitive predominant (57%) Neuro-psychiatric predominant (27%) Parkinsonism predominant (16%)

PD: parkinson's disease. Dx: diagnosis. HY: Hoehn and Yahr. PPMI: Parkinson's Progression Marker Initiative. NS: not stated. RBD: REM sleep behavior disorder (either reported of polysomnogram proven)
Gray boxes indicate variables used to determine clusters.
[a]PROPARK cohort from Verbaan D, Marinus J, Visser M, et al. Cognitive impairment in Parkinson's disease. J Neurol Neurosurg Psychiatry 2007;78:1182–1187.
[b]Probable DLB from McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863–1872.
[c]Derived from cluster averages.
[d]Motor parkinsonism derived from chart review, not UPDRS parts II and III.

TABLE 2. Phenotypic Differences in LBD by Neuropathologic Subtype

	PD/PDD		DLB	
	SYN-AD	SYN + AD	SYN-AD	SYN + AD
Age of onset, (range of mean age)	Younger (57–66)	Older (68–74)[21,25,65,69,94,97]	Similar (68–78)	Similar (70–85)[21,a,29,94,a]
Motor dementia Interval, (range of mean years)	Longer (8–15)[b]	Shorter (2–10)[21,32,69,97,c]	NA	
Survival (range of mean years)	Longer[a] (10–19)	Shorter (4.5–13.0)[21,25,65,69,97,98]	Longer (6–10)	Shorter (3–7)[21,a,29,94,a]
Motor phenotype	More prominent rest tremor	Greater relative postural instability gait disorder[25,32,106]	No clear data examining influence of AD copathology, but overall DLB has less common rest tremor and more prominent postural instability[114,132]	
Hallucinations/fluctuations	No clear data comparing influence of AD copathology, but hallucinations/ fluctuations are common in PDD[14]		More frequent	Less frequent[13,31,103]
Cognitive dysfunction	Executive, attention, visuospatial deficits	Additional episodic memory, naming deficits[3,105]	Executive, attention, visuospatial deficits	Additional episodic memory, naming deficits[94,104,105]
Genetic associations[d]	*GBA* mutation carriers ++ APOE ε4 allele carriers +	*GBA* mutation carriers +[221] APOE ε4 allele carriers ++[16,226-228]	*GBA* mutation carriers ++, APOE ε4 allele carriers +	*GBA* mutation carriers +,[214,221] APOE ε4 allele carriers ++[212,226-228]

[a]Not published data.
[b]Some studies also describe small groups of patients with SYN-AD pathology and a more fulminant course.[69,95,103,107]
[c]Several studies do not directly report motor dementia interval, but rather cite that PDD patients are more likely to harbor SYN + AD pathology rather than SYN-AD.[2,25,32,66,69]
[d]Both GBA pathogenic variants and APOE4 allele have been linked to LBD with greater frequency compared to the general population;[212,214,221,226-228] + (less common) /++ (more common) denote relative frequency of genetic variant between SYN-AD and SYN+AD subgroups.
SYN-AD, synuclein neuropathology with no or low level AD copathology; SYN + AD, synuclein pathology with moderate- or high-level AD copathology; NA, not applicable, DLB clinical syndrome defined by motor dementia interval ≤1year.

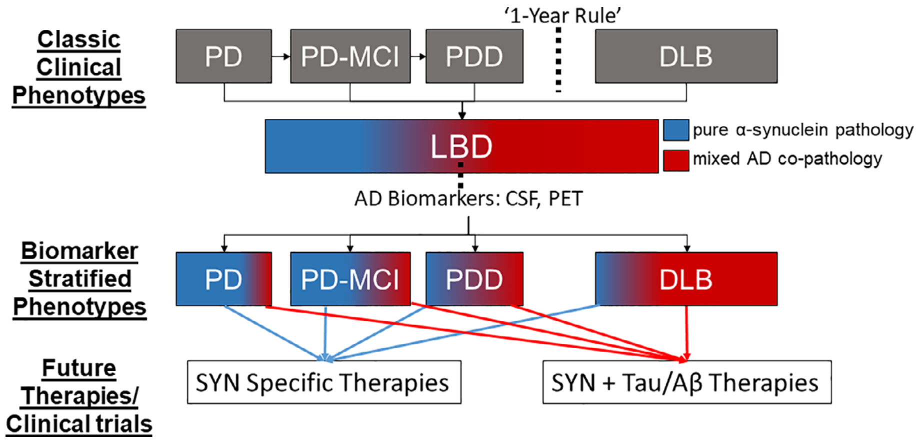

FIG. 1. Current criteria separate lewy body disorders (LBDs) into Parkinson's disease (PD) and dementia with Lewy bodies (DLB) on the basis of the "1-year rule" (dashed line). Within LBD, neuropathology ranges from pure synucleinopathy (SYN only: blue) to those with clinically significant AD copathology (SYN + AD: red). Emerging biomarker data suggest that AD copathology may be accurately detected in living patients, and we illustrate here a potential strategy to stratify clinical cohorts of LBD by the AD biomarker profiles (dashed lines) to improve clinical trials for SYN and Tau and/or Aβ directed therapies during life for LBD patients (shaded clinical phenotype boxes represent relative frequency of pure SYN or mixed AD copathology in large autopsy series in PD, Parkinson's disease dementia (PDD), and DLB). PD-MCI, PD with mild cognitive impairment.

occipital regions[37,194] with unique areas of uptake in the primary motor and sensory cortices,[195] as opposed to temporal and frontal lobes as observed in AD. These data show many similarities to our recently published postmortem work using digital histological methods.[94] Increased ^{18}F-flortaucipir uptake in LBD is associated with cognitive deficits across PD, PDD, and DLB.[37,196] Postmortem validation studies of ^{18}F-flortaucipir in LBD are needed to confirm these in vivo observations and further clarify the regional distribution and cognitive phenotypes associated with tau pathology in LBD. Nonetheless, these divergent patterns of uptake in LBD compared with AD could potentially be interpreted as consistent with the aforementioned model data suggesting cross-seeding of SYN, tau, and Aβ by specific alpha-synuclein strains.[54-57] Moreover, the intermediate degree of ^{18}F-flortaupcipir uptake in LBD between healthy controls and AD is consistent with our observations using digital histological measurements of tau pathology in LBD and AD.[94]

Genetic Influences

Monogenic causes of LBD, including mutations, duplications, and triplications of the *SNCA* gene as well as mutations in *PARKIN*, *PINK1*, *DJ-1*, and others, are rare in PD and DLB.[197-203] More common genetic risk factors for the development of LBD include the *MAPT* H1 haplotype,[206-209] apolipoprotein epsilon ε4 alleles (*APOE ε4*),[210-215] and the glucocerebrocidase gene (*GBA*)[17,199] and leucine-rich repeat kinease-2 (*LRRK2*).[216,217] *MAPT* H1 haplotypes have been associated with greater risk of occurrence of PD and DLB[218-220] and dementia in PD[221,222] and may be associated with higher degree of SYN pathology at autopsy.[223,224] Certain studies have not found an association of H1 haplotypes with DLB,[225] and, additionally, one other study has documented decreased in AD copathology in DLB associated with H1 haplotypes.[226] *APOE ε4* alleles in LBD have been associated with higher likelihood of both tau and Aβ copathology and also higher degrees of SYN,[16,209,227-229] a higher risk of developing dementia,[208,230,231] and altered cognitive performance on specific tests.[208] *GBA* mutations have been associated with earlier-onset PD and a more rapidly progressive clinical course with a 6-fold higher risk of dementia.[17,201,232-234] Autopsy data show relatively greater neocortical synucleinopathy burdens in patients with *GBA* mutations than sporadic PD with variable rates of AD copathology.[235-237] *LRRK2* mutations are not associated with a more aggressive clinical course of PD, although one study of young patients showed an association with the PIGD phenotypes.[186,187] Postmortem studies of brains from patients with *LRRK2* mutations have found mixed SYN, tau, and transactive response DNA binding protein 43 kDa (TDP-43) neuropathologies.[216,238] In some patients with *LRRK2* mutations and also in patients with other, more rare, monogenic causes of PD, SYN pathology can be absent even in the setting of severe clinical phenotypes.[238] Genome-wide association studies (GWAS) comparing statistical frequencies of single-nucleotide polymorphisms (SNPs) between disease and control populations are an important mechanism for discovery of novel common risk variants. Two recent GWAS in DLB that had pathological validation in a subsection of their subjects confirmed the strong effect of *APOE ε4* alleles, *GBA*, and *SNCA* genes in the occurrence of DLB,[209,225] similar to other studies in PD.[218,220] SNPs in *SNCA* have been linked to increased *SNCA* gene expression in sporadic PD.[204] Interestingly, SNPs in the *SNCA* gene that associated with PD in previous studies were different than the ones implicated in the occurrence of DLB.[218,225] Thus, there are both shared and distinct risk SNPs implicated in DLB compared to PD and AD, likely contributing to the clinicopathological spectrum of LBD. These GWAS studies have also highlighted potential roles for other genes coding for proteins related to antigen presentation (*HLA-DPA1/DPB1* and *DRB5*),[218,220,239] tyrosine kinases (*GAK*),[220,240] cell adhesion molecules (*CNTN1*),[225] lysosomal degradation (*SCARB2, TMEM175*),[209,241] synuclein processing (*SPTBN1*),[239] vesicular transport (*SYT11*),[220,240] and many others in the potential pathogenesis of LBD, although their role in disease progression and neuropathology remains to be seen. Finally, emerging studies highlight SNP associations with cognitive and motor features in sporadic PD,[205,208] suggesting that common genetic variation may also influence clinical heterogeneity in LBD.

Conclusion

LBDs comprise a complex spectrum of clinicopathological entities with marked clinical heterogeneity and a common neuropathology of misfolded alpha-synuclein aggregating into Lewy bodies, Lewy neurites, and variable amounts of tau and Aβ pathology. Here, we review multiple converging lines of evidence from CSF measurements, PET imaging, and neuropathological studies emphasize the importance of co-occurring tau and Aβ pathology affecting the clinical features and course of LBD (Table 2). Although lower in overall burden compared to AD, tau in particular appears to have a strong influence on dementia and survival. We are optimistic that detailed neuropathological studies of SYN, Aβ, and tau, using increasingly sophisticated techniques, will continue to improve the understanding of how the mixed neuropathology in LBDs can be accurately predicted by precisely measured ante mortem biomarkers compared with the current strictly clinical system of classification. Whereas the neuropathology in LBD is likely a spectrum, postmortem work reviewed here suggest those patients with moderate- to high-level AD neuropathological change at death have a worse prognosis and altered clinical phenotypes. Such patients can be currently identified using emerging biomarkers, and we propose that AD biomarker profiles be included in research categorization of LBD. This proposed formulation has the potential to put the assignment of patients participating in well-designed therapeutic or disease-modifying clinical trials of the future on firmer molecular biological footing. Indeed, stratifying classical LBD clinical phenotypes (PD, PD-MCI, PDD, and DLB) by the presence of absence of in vivo biomarkers of AD pathology, in a manner similar to those proposed in AD dementia,[242] will improve prognostication and potentially improve statistical power of clinical trials for both symptomatic and disease-modifying therapies by providing more homogenous patient populations (Fig. 1). Moreover, based on growing experimental and human pathology data suggesting synergistic association of AD and SYN pathology, it is possible LBD patients with mixed pathology may benefit from AD-directed therapies as they are developed.

Although neuropathology observed in LBD postmortem represents a spectrum of both SYN and AD pathology, the factors that influence the occurrence of these pathologies is unclear. Age, genetic influences, or potentially different strains of pathogenic alpha-synuclein may partially account for divergence in LBD patients who develop significant AD copathology and possibly the rate of progression of these pathologies. Factors that result in varying expression of these pathologies are also poorly understood. Longitudinal, prospective studies of LBD patients, using multimodal biomarkers followed to autopsy, will aid in beginning to answer these questions. Other copathologies, including cerebrovascular disease and TDP-43, are likely to influence clinical features and progression in LBD as well[243]; however, they require further study. The majority of existing LBD studies focus on either PD/PDD or DLB separately, based partly on separate referral patterns to movement disorders specialists and memory clinics respectively. We suggest that harmonized assessments of PD, PDD, and DLB cohorts followed to autopsy are urgently needed to capture the full clinicopathological spectrum of LBD and further elucidate the underlying biological substrates for clinical heterogeneity. ■

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