DLB and PDD boundary issues: Diagnosis, treatment, molecular pathology, and biomarkers

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Abstract—For more than a decade, researchers have refined criteria for the diagnosis of dementia with Lewy bodies (DLB) and at the same time have recognized that cognitive impairment and dementia occur commonly in patients with Parkinson disease (PD). This article addresses the relationship between DLB, PD, and PD with dementia (PDD). The authors agreed to endorse "Lewy body disorders" as the umbrella term for PD, PDD, and DLB, to promote the continued practical use of these three clinical terms, and to encourage efforts at drug discovery that target the mechanisms of neurodegeneration shared by these disorders of α-synuclein metabolism. We concluded that the differing temporal sequence of symptoms and clinical features of PDD and DLB justify distinguishing these disorders. However, a single Lewy body disorder model was deemed more useful for studying disease pathogenesis because abnormal neuronal α-synuclein inclusions are the defining pathologic process common to both PDD and DLB. There was consensus that improved understanding of the pathobiology of α-synuclein should be a major focus of efforts to develop new disease-modifying therapies for these disorders. The group agreed on four important priorities: 1) continued communication between experts who specialize in PDD or DLB; 2) initiation of prospective validation studies with autopsy confirmation of DLB and PDD; 3) development of practical biomarkers for α-synuclein pathologies; 4) accelerated efforts to find more effective treatments for these diseases.

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The diagnostic designation of dementia with Lewy bodies (DLB) was formalized in 1996 to bring attention to a group of patients with symptoms that differ from those of Alzheimer disease (AD) and vascular dementia.[1] Since then, and with increased recognition by clinical researchers, DLB is now considered to be the second most common subgroup of dementia,[1] with widespread Lewy bodies occurring in more than 20%[2,3] and focal Lewy body formation in nearly 50% of dementia patients.[4] In parallel, cognitive impairment in idiopathic or Lewy body PD occurs early and becomes an important nonmotor feature of the disease in its later stages. The term Parkinson disease dementia (PDD) has been applied to this frequent complication of the typical motor disorder.[5]

The discovery of α-synuclein as a component of PD pathogenesis in 1997[6] gave PDD and DLB a common biologic theme, spurring interest in the relationship between these disorders. The third report of the DLB Consortium[7] made a brief statement about the PDD/DLB interface to 1) highlight the overall clinical and pathologic similarities between the two syndromes; 2) reinforce the need to make a clinical distinction between DLB and PDD, using the timing of the onset of cognitive symptoms in relation to motor symptoms (1 year or less = DLB; more than 1 year = PDD) as the basis; and 3) recognize the need to address boundary issues in more detail. This ongoing debate prompted the formation of the current DLB/PDD Working Group. Here, we address boundary issues

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as an extension of a global concerted effort to fully understand the Lewy body diseases (LBDs).

Clinical. When the hallmark clinical features of the Lewy body disorders are present, our diagnostic specificity is high. Specialists in movement disorders regularly follow patients with PD for years before cognitive dysfunction becomes noteworthy enough to suggest the onset of dementia. However, the definition of when cognitive decline in PD is sufficient to constitute dementia needs to be clarified. Specialists in cognitive disorders evaluate dementia patients with the classic symptoms of DLB, which allow clinicians to distinguish the Lewy body disorders from other dementia subtypes. Difficulty with diagnosis arises when patients fall in between the two classic profiles of DLB and PDD. Distinguishing the Lewy body disorders from non-Lewy body dementias remains difficult when atypical presentations occur.[8-10] Non-Lewy pathology, particularly the neurofibrillary degeneration of AD, may obscure the clinical features of the Lewy body disorders when the two pathologies occur together (e.g., LBVAD) and dominate the clinical picture with features of AD instead of DLB.[11] Vascular pathology is also frequent in DLB[10] and can also potentially modify symptoms and signs. In addition, differences between all dementia subtypes are stage dependent with greater overlap in clinical features between all dementia groups in advanced disease. Although diagnostic criteria have not yet been defined for PDD, similar issues blur the boundaries that "separate" these disorders.

Many patients fall into an overlapping "gray zone" because DLB patients may present with parkinsonism around the same time as the cognitive symptoms, and early cognitive change is recognized in PD. In addition, there is no clinical symptom that absolutely distinguishes DLB and PDD as both may have psychiatric symptomatology, autonomic symptoms, REM-sleep behavior disorder,[12] cognitive fluctuations, and neuroleptic sensitivity reactions.[13] The neuropsychological profiles in PDD and DLB share basic similarities including prominent abnormalities in attention, executive function, visuospatial function, language function, memory retrieval, and behavior.[14-19]

However, differences in clinical features have been described in studies of DLB and PDD patients characterized by consensus criteria. Subtle cognitive differences have been found between PDD and DLB, with DLB subjects making more conceptual and attentional errors than PDD subjects, even after controlling for dementia severity.[14,20] Psychiatric symptoms that differ quantitatively more than qualitatively occur in DLB and PDD, with DLB patients having more hallucinations and psychoses than those with PDD.[17,21] Adverse reactions to antipsychotic agents may also be more frequent in DLB, whereas patients with PDD are more likely to be taking a wider variety of potentially psychotogenic doses of antiparkinson drugs.[13] Saccadic eye movements are similar in DLB and PDD.[22] PDD subjects have more asymmetry in motor features, at least initially, and DLB subjects tend to have fewer signs of parkinsonism, although the majority of DLB patients eventually develop parkinsonism characterized by generalized slowing and postural and gait disturbances, without prominent tremor.[23]

The clinical diagnostic criteria set forth in the third DLB consensus conference[7] can be applied to PDD, although there are no published validation studies. The need exists for 1) a clear definition statement on the diagnosis of PDD to enable research progress and large-scale studies and 2) improved methods for defining and distinguishing the relative functional contributions of cognitive and motor impairment to overall disability. A Movement Disorder Society Task Force is currently developing diagnostic criteria for PDD. Once these criteria are established, additional prospective studies involving both PDD and DLB subjects are needed to clarify the similarities and differences in clinical features in these disorders.

Cellular and molecular pathology. The presence of widespread Lewy bodies differentiates the Lewy body disorders from other dementia subtypes. Cortical Lewy bodies and Lewy neurites are often widespread in PDD and DLB and correlate with the severity of the dementia.[24,25] and DLB cases almost always have limbic Lewy bodies; however, spread of Lewy bodies to neocortical areas in high quantities is uncommon in PD subjects in the absence of cognitive impairment. There are no hallmark neuropathologic features that distinguish PDD from DLB, in part because most patients die with end-stage disease at which point the brain is diffusely involved and clinical phenotypes of the two disorders are indistinguishable. The brain regions where pathologic differences occur include the substantia nigra (where neuronal loss is greater in PDD than DLB) and possibly the striatum (where α-synuclein pathology may be greater in DLB than PDD).[26]

Pathologic substrates of PDD and DLB are heterogeneous and include neuronal loss, basal forebrain (cholinergic) degeneration, AD, and vascular pathology in addition to Lewy body pathology. β-Amyloid pathology is a more consistent feature of DLB, and a recent study demonstrated that diffuse plaques, resembling those that typify DLB, are associated with subtle impairments in cognition in AD.[27] The influence of β-amyloid pathology, if any, on the clinical phenotype in the Lewy body disorders is unknown. However, neuritic AD pathology strongly affects clinical phenotype in DLB.[11,28]

α-Synuclein aggregates into fibrils in Lewy bodies and Lewy neurites in PDD, DLB, and PD.[29] The structure of the Lewy body is indistinguishable in all three conditions, with α-synuclein as its principal pathologic protein. Solubility and epitope studies show similar features in α-synuclein between diseases.[29] Although the brainstem and olfactory system are the

first and most common regions to undergo neurodegeneration in PD, the disorder is often clinically unapparent at that stage and only becomes clearly symptomatic when the substantia nigra and other midbrain nuclei are affected. Later, multiple additional brain regions are affected as these disorders progress so that their clinical manifestations commonly extend beyond those attributable to the nigrostriatal system alone.[30,31] As such, PD, DLB, and PDD may be different points on a continuum with motor and nonmotor features reflecting the regional burden and distribution of pathology.

Factors that determine the regional distribution of pathology in relation to the symptoms of DLB, PDD, and PD are incompletely understood. Age may play a role in regional susceptibility because younger individuals are more likely to present without cognitive impairment (pure PD), whereas meaningful cognitive change (either PDD or DLB) occurs in the older adult. Hallucinations in DLB are associated with Lewy body counts in posterior temporal regions.[32] The greater executive dysfunction in DLB has been associated with disruption of medial temporal lobe projections to frontal regions. Differential striatal pathology may account for some of the differences in motor features and motor responses to medications with differences in the burden of Lewy pathology,[26] the regional distribution and severity of dopaminergic losses, and the level of dopaminergic upregulation. Preliminary results from a recent autopsy study of patients with PDD show that brain pathology is similar to that of DLB (with Lewy pathology and AD changes) if dementia began within 10 years of PD onset, whereas in PD patients with onset of dementia more than 10 years after PD onset, morphologic changes were less pronounced and the more prominent finding was a marked cholinergic deficit.[33] These results, if substantiated, call into question the 1-year rule that currently distinguishes DLB from PDD.

Overall, there are multiple reasons to implicate Lewy bodies and pathologic species of α-synuclein in PD, PDD, and DLB:

1. Mutations/multiplications in the *α-synuclein* gene cause familial PD/PDD/DLB.
2. Lewy bodies and Lewy neurites are hallmark PD/PDD/DLB amyloids detected by α-synuclein–specific antibodies.
3. Epitope mapping demonstrates that regions spanning α-synuclein are present in Lewy bodies.
4. Filamentous α-synuclein aggregates in Lewy bodies and Lewy neurites contain abnormally nitrated, phosphorylated, and ubiquitinated residues.
5. α-Synuclein filaments are recovered from PD/PDD/DLB brains as well as from Lewy bodies purified from these brains.
6. Recombinant α-synuclein forms Lewy body–like amyloid fibrils and amino acids 71 to 82 in α-synuclein are essential for filament assembly.
7. α-Synuclein single transgenic mice/worms/flies develop a neurodegenerative disease with filamentous α-synuclein amyloid deposits.
8. Cortical Lewy bodies detected with antibodies to α-synuclein correlate with dementia in PDD/DLB.
9. Double transgenic mice overexpressing human familial AD mutant amyloid precursor proteins (APPs) and α-synuclein show an augmentation in α-synuclein pathologies.
10. Coexpression of heat shock proteins with α-synuclein in flies and β-synuclein with α-synuclein in mice ameliorates the disease phenotype, whereas induction of heat shock proteins with geldanamycin in α-synuclein transgenic flies attenuates degeneration of Lewy body–containing neurons.

The mechanism by which α-synuclein leads to neuronal death is the subject of intense investigation. α-synuclein is abundant in the normal brain at the synaptic terminal. It may regulate dopamine release or work with other molecules to protect presynaptic nerve terminals from injury. Because Lewy body pathology is composed of fibrillar α-synuclein and several autosomal dominant mutations in *α-synuclein* lead to enhanced rates of protein fibrillization, this conformational change in the structure of α-synuclein may render it neurotoxic. Some investigators have proposed that small, prefibrillar oligomers of α-synuclein are the toxic species leading to neuron dysfunction and degeneration. Conversely, the sequestration of this synaptic protein into inclusions may result in the loss of a critical biologic function leading to cell toxicity. α-Synuclein accumulations in synaptic regions may lead to lysosomal leakage and signaling abnormalities. Serine 129 (Ser129) is an important phosphorylation site for α-synuclein in all the Lewy body disorders, and antibodies specific to phosphorylated α-synuclein have been shown to specifically recognize Lewy bodies and Lewy neurites.[34] Dopamine is another factor that affects α-synuclein structure, inducing α-synuclein to form soluble oligomers and reducing insoluble fibrils.[35,36] The presence of truncated C-terminal forms of the α-synuclein molecule or its proteolysis are likely to affect the initiation of α-synuclein aggregation as well as the continuation of aggregation in these disorders.[37] Cell culture and animal model studies will continue to illuminate key underlying mechanism(s) that can serve as targets for intervention.

Proteins not directly related to α-synuclein, such as heat shock proteins and other chaperone proteins, also undoubtedly affect pathogenesis of the Lewy body disorders.[38] Inflammation is also likely to be a relevant contributor to the neurodegenerative cascade in Lewy body disorders. Because the relationships between these cascades and the LBD process is largely unknown, translational research involving non–α-synuclein–related cascades should be encouraged. Also, research relating to aggresome formation and other processes involved in protein degradation

are worthy of further investigation.[39,40] Research addressing the cellular and molecular basis of overlap (AD and vascular) pathology in PDD and DLB may have important implications. For example, the common co-occurrence of β-amyloid and α-synuclein raises the possibility of a major pathogenic mechanism between APP and α-synuclein aggregation.[41]

Genetics. Parkinsonism and the associated dementia are occasionally inherited. Genetic abnormalities involving the *α-synuclein* gene on chromosome 4 may lead to either PD or PDD.[42-46] Mendelian genetic studies reinforce the position that even with fully penetrant, autosomal dominant mutations, clinical phenotypes often differ. For instance, extra copies of the *α-synuclein* gene may lead to either PD (PDD) or DLB,[44-47] and it has been speculated that this variable expression is due to a dose effect.[47] Because the basic pathogenic mechanism is often similar in genetic and sporadic diseases, it is feasible that the fundamental pathogenesis of Lewy body formation in sporadic PDD and DLB is similar in cases with genetic abnormalities of the *α-synuclein* gene.

The concept of Lewy body PD as an etiologically distinct movement disorder was strongly reinforced by the identification of *α-synuclein* mutations in autosomal dominant PD[6] and by the demonstration that pathologically altered forms of α-synuclein are the major building blocks of the filaments aggregating to form Lewy body and Lewy neurite pathology.[48] This notion was supported by the subsequent identification of additional *α-synuclein* mutations and Lewy body pathology in kindreds with other clinical manifestations of disease ranging from typical PD (without dementia) to parkinsonism with PDD and to DLB.[7,30,31] Each of these clinical entities is characterized by widespread Lewy bodies and related α-synuclein pathologies such as dystrophic Lewy neurites.[46,49,50] Thus, these discoveries have dramatically changed concepts of the role of Lewy bodies in mechanisms of disease, and it now is clear that the accumulations of pathologic species of α-synuclein and the deposition of α-synuclein fibrils into inclusions result in the formation of diagnostic signatures of α-synuclein opathies, but, more importantly, there is evidence that these pathologies play integral roles in the onset and progression of PD and related disorders.

Dominantly inherited forms of AD (mutations in the APP and presenilin-1 genes) often have Lewy body pathology, suggesting that genetic abnormalities unrelated to α-synuclein may also promote aggregation of α-synuclein.[51] Also, brains from individuals with Down syndrome often contain Lewy bodies.[52] Mutations in leucine-rich repeat kinase 2 (LRRK2) gene, a more common genetic cause of PD (sometimes with dementia), may lead to α-synuclein, tau or ubiquitin pathology (with or without Lewy bodies).[53] These data suggest that genetic causes of abnormal protein processing or other types of cellular damage can cause aggregation of a variety of CNS proteins, and they underscore the need for additional genome-wide screening to identify susceptibility genes for DLB/PDD.[54] Thus, there are multiple genetic factors, even some unassociated with α-synuclein, that can trigger the formation of Lewy bodies, irrespective of the disease phenotype.

The combination of dementia and parkinsonism does not always reflect α-synuclein pathology. Mutations of the tau gene on chromosome 17 may also show PDD or DLB clinical phenotypes, but these cases lack Lewy bodies and have clinical and neuropsychological features different from PDD or DLB (reviewed in Ghetti et al.[55]).

Biomarkers. Clinical and neuropsychological abnormalities differentiate Lewy body disorders from AD to some extent, as noted above, but the utility of other biomarkers has been investigated to improve diagnostic accuracy and sharpen the distinction between PDD, DLB, and other dementias. MRI does not appear to be a reliable means for discriminating between AD and the Lewy body disorders,[56,57] although one study suggests that the volume of the putamen may help differentiate AD from DLB.[58] Longitudinal volumetric MRI studies can sensitively monitor disease progression in DLB and PDD. Functional imaging with PET may be useful for determining the distribution of disease. Pittsburgh Compound B (PIB) PET is potentially valuable for determining the β-amyloid load[59,60] and may aid in determining β-amyloid burden associated with PDD and DLB alongside PET measures of cholinergic and glucose metabolic impairment. β-Amyloid levels may be greater in DLB than in PDD cases. Dopamine transporter imaging of nerve terminals in the striatal caudate–putamen complex can sensitively discriminate diseases with dopamine deficiency from other degenerative dementias, but vascular dementias can also affect the integrity of the striatal nerve terminals.[61]

Cortical cholinergic deficits and other alterations of the cholinergic system, associated with degeneration of the basal forebrain, are prominent in PDD and DLB and more severe than cortical cholinergic losses in other dementia subtypes such as AD, vascular dementia, or frontotemporal dementia.[62,63] They are linked to key clinical symptoms such as attentional dysfunction, fluctuations, and visual hallucinations and may be an early marker of pathology because cholinergic abnormalities also occur in PD subjects who are cognitively normal.[64] PET tracers specific for acetylcholinesterase are in development and have potential use as biomarkers for these disorders.[65,66]

There is a clear need for α-synuclein and Lewy body biomarkers. CSF biomarkers are available for tau and β-amyloid, but there are no validated biomarkers for α-synuclein aggregation. Oligomeric α-synuclein is a potential biomarker in the blood.[67] In the future, it will be essential to develop a nonpeptide SPECT or PET ligand for α-synuclein aggregates to assess Lewy body load in DLB and PDD.

The regional distribution of such a ligand may also help identify differences between DLB and PDD. However, this will be more difficult than in vivo imaging of amyloid plaques due to the intracellular location of Lewy bodies. CSF, blood, and imaging biomarkers will be valuable as a means to assess risk, follow disease course, and monitor response to treatments.

Treatment. Symptomatic treatment with cholinesterase inhibitors is currently the only treatment strategy for the cognitive symptoms of both PDD and DLB with demonstration of modest efficacy in several randomized, placebo-controlled, double-blind studies.[68-71] The largest randomized studies have used rivastigmine (up to 12 mg/day) in subjects with mild to moderate disease.[69,70] The benefits of rivastigmine on cognitive and behavioral symptoms have been comparable for patients with PDD and DLB. Attentional measures particularly improved in both disorders.[69,72] Adverse events were similar, with nausea and vomiting being the most common side effects in both PDD and DLB. Rivastigmine was reported to worsen tremor in 10% of the patients with PDD, although average Unified Parkinson's Disease Rating Scale scores were not significantly different between treatment and placebo groups. It is unknown whether there are subtle differences in the response to cholinesterase inhibitors between DLB and PDD groups because only relatively small studies have been done.[73] Donepezil has also been studied in PDD in two small randomized, controlled trials,[68,71] but no studies have compared efficacy or tolerability of the different cholinesterase inhibitors in a head-to-head comparison.

The small risk of worsening parkinsonism and the relatively poor CNS selectivity of the cholinesterase inhibitors agents are potentially limiting factors.[74] Dose-response relationships have been defined for these agents[75] with a report of rebound worsening of symptoms on rapid withdrawal.[76] PET tracers of cholinesterase inhibition may aid in drug development and in future clinical trials for PDD and DLB. Cholinergic enhancement strategies currently are seen as symptomatic therapies, and there is no evidence of a neuroprotective effect in PDD or DLB. In addition, these agents may prove to be useful when used in conjunction with agents offering a different mechanism of action. For example, glutamate receptor modulation using agents such as memantine may prove to be of benefit, although there are anecdotal reports of worsening in DLB patients.[77-79]

Dopaminergic therapy, particularly with levodopa, is the current mainstay of therapy for the motor features of PDD/DLB, although the effect may be less pronounced in PDD than in PD, and no controlled studies have been reported in DLB. Potential side effects in cognitively impaired patients, such as psychotic symptoms and delirium, should be balanced against potential motor improvements with these drugs.[80]

The safety and tolerability of all medications used to treat PDD and DLB and sensitivity to neuroleptic agents need to be assessed. Although investigators and clinicians believe that certain (not all) atypical antipsychotic agents are sometimes necessary and useful for the psychotic symptoms in DLB and PDD, these agents should be used with caution due to a risk of side effects and worsening of both motor and cognitive functioning in PDD and DLB.[13]

α-Synuclein aggregation should be a major target for drug discovery for both the motor and cognitive features of PDD and DLB.[81] Improved animal models are required to further advance drug discovery and elucidate the underlying disease mechanisms because current animal models have been inadequate for predicting neuroprotective therapeutics. Strategies for treatment based on pathogenesis include developing therapies that prevent α-synuclein misfolding, fibril formation, and aggregation. Alternative strategies include identifying trophic factors or neuroprotective agents that shield synaptic structure and function.

The frequent presence of β-amyloid in the synucleinopathies, especially DLB, raises the possibility of a link between α-synuclein and APP misprocessing.[41] Hyperphosphorylated forms of tau are also frequently observed in the LBD brain. As such, APP (and possibly tau) could also be viewed as potential therapeutic targets for these disorders.

Summary and discussion: Recurrent themes and future directions. The Working Group agreed unanimously that PDD and DLB are more similar than different. The main difference between the two entities is the timing of onset of dementia in relation to motor symptoms. There was agreement that the 1-year rule serves a pragmatic purpose and should be retained until further research and dialog force a change in definition. Despite this somewhat arbitrary distinction, the clinical manifestations of DLB and PDD reflect a common pathobiology, presumably related to misfolding and toxic aggregation of α-synuclein. Therefore, we recommended to adopt two classification systems in parallel: a multiple disorder model that distinguishes between PDD and DLB for clinical classification and a single disorder model of LBD for classifying the underlying disease mechanisms. For routine patient care, clinical interventions and clinical research, a distinction remains important between patients with a primary symptom complex of dementia and those with a primary movement disorder. The term Lewy body disorders is preferable when researching the underlying biology because the presence and composition of Lewy bodies is similar in both PDD and DLB.[31] It may also serve as a clinical term when there is a need to differentiate DLB/PDD from AD and other non–Lewy body dementias. The consensus among participants at the DLB-PDD workshop was to sanction the term Lewy body disease as an umbrella term for studying the biology of these disorders (PD, PDD, and DLB), but

Table *Terms and abbreviations for the Lewy body disorders*

Term	Abbreviation
Dementia with Lewy bodies	DLB
Parkinson disease	PD
Parkinson disease with dementia	PDD
Lewy body dementias (PDD and DLB)	LB dementias
Lewy body disease (PD, PDD, and DLB)	LBD

to maintain the three individual terms for clinical and some scientific needs. We also agreed on the use of abbreviations for these disorders, as described in the table.

We believe that there are appropriate clinical and neuropathologic diagnostic criteria for DLB,[7] but anticipate large, prospective clinicopathologic correlation studies to validate and refine these criteria. It may be possible to adopt the newly proposed pathologic assessment of DLB for the neuropathologic assessment of PDD as well. Although motor impairment complicates cognitive assessment, a clear clinical definition of PDD is needed, including clinical tools that can be applied across centers to evaluate motor, neuropsychological, psychiatric, and activities of daily living function. The Movement Disorder Society's Task Force on Diagnostic Criteria for PDD should harmonize with current DLB diagnostic criteria. The Task Force is expected to have criteria ready by late 2006 or early 2007. Criteria for PD psychosis are also under way. Once diagnostic PDD criteria are established, multicenter, prospective collaborations involving PDD and DLB groups can be organized to investigate a number of pressing questions, including 1) whether clinical phenotype differences are related to regional distribution of anatomic and biochemical pathology; 2) whether early pathology underlying DLB and PDD differ; 3) whether there is a sequence of pathologic features peculiar to Lewy body disorders including the quantity and tempo of associated AD and vascular pathologies; 4) whether Lewy neurites, Lewy bodies, neurochemical changes, or other pathology correlate with cognition; and 5) whether Lewy body pathology correlates with fMRI, PET, and other biomarkers.

The central view of the (α-synuclein–containing) Lewy body as being a principal marker of pathology in primary Lewy body disorders is supported by the evidence cited above. However, the mechanism whereby α-synuclein leads to neurodegeneration is unclear, although several possibilities have been proposed.[30,31,82-84] Irrespective of the mechanism of pathogenesis, there is increasing evidence implicating increased expression of α-synuclein in the pathogenesis of both familial and sporadic PD. Thus, duplication and triplication of *α-synuclein* lead to a gene dose–dependent increase in disease severity and decrease in age at onset.[47] Furthermore, genetic polymorphisms in the *α-synuclein* gene may be a risk factor for sporadic PD by increasing the expression of α-synuclein. Because mutations or duplications in the gene for α-synuclein lead to genetic forms of autosomal dominantly inherited PD, PDD, and DLB, increased expression, aggregation, and accumulation of α-synuclein in the brain appear to play a key role in the pathogenesis of neurodegeneration.[31,32,84] Further support for the role of α-synuclein in disease has come from transgenic mice and other model systems engineered to overexpress mutant forms of α-synuclein, which show both α-synuclein pathology and neurodegeneration.[82,85] Importantly, in human disease, deposition of brain α-synuclein may precede disease symptoms by more than a decade, providing a window for neuroprotection or neurorescue.[31] However, environmental factors may also play a crucial role in the pathogenesis of α-synucleinopathies, and epidemiologic studies suggest an association of PD with environmental toxins such as pesticides. Indeed, long-term systemic treatment of rats with rotenone, a pesticide known to inhibit mitochondria, causes selective nigrostriatal dopaminergic degeneration with associated inclusions containing fibrillar α-synuclein.[84,86] Rotenone treatment may induce an increase in oxidative stress in the dopaminergic neurons, which in turn may facilitate fibrillization of α-synuclein, providing a link between oxidative stress and pathogenesis of α-synucleinopathies.

For the future, the PDD/DLB Working Group agreed that the three most important research priorities include 1) continued contact between dementia and movement disorders clinical and research groups; 2) conducting prospective validation studies of DLB and PDD; and 3) development of clinical biomarkers for α-synuclein/Lewy body aggregation in the human brain. For studies of early diagnosis, prevention, and neuroprotective intervention, a DLB/PDD equivalent of mild cognitive impairment (MCI), analogous to the role of MCI as a precursor of AD,[87] needs to be defined. The reasons for gender differences between the Lewy body disorders (which are male predominant) and female-predominant AD are poorly understood. Understanding the reason for the age-related selective vulnerability such that young individuals almost exclusively develop a PD phenotype may also lead to important insights regarding the Lewy body disorders. Risk factors for DLB and PDD have not been clearly defined. Population-based studies of the international distribution of disease and its determinants, incorporating common methodologic approaches for clinical diagnosis, risk factor assessment, and prospective follow-up, including postmortem validation of diagnosis, will be critical. Similar studies may also determine whether the development of cognitive impairment is inevitable in PD and further define what genetic or environmental factors impact risk.

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Appendix

The working group includes the following participants: Dag Aarsland, MD, Stavanger University Hospital, Stavanger, Norway, and the Institute of Clinical Medicine, University of Bergen, Bergen, Norway; Brad Boeve, MD, Mayo Clinic, Rochester, MN; David J. Brooks, MD, Imperial College School of Medicine, Hammersmith Hospital, London, UK; Dennis W. Dickson, MD, Mayo Clinic Jacksonville, Jacksonville, FL; Bruno Dubois, MD, Hopital La Salpetriere Federation Neurologie, Paris, France; John Duda, MD, Philadelphia VA's Parkinson's Disease Research, Education, and Clinical Center, Philadelphia, PA; Murat Emre, MD, Istanbul Faculty of Medicine, Department of Neurology, Istanbul, Turkey; Stanley Fahn, MD, Neurological Institute, New York, NY; Jennifer Farmer, University of Pennsylvania School of Medicine, Philadelphia, PA; Douglas Galasko, MD, UCSD, San Diego, CA; Jim Galvin MD, MPH, Washington University, St. Louis, MO; Christopher G. Goetz, MD, Rush University Medical Center, Chicago, IL; Murray Grossman, MD, Hospital of University of Pennsylvania, Philadelphia, PA; John H. Growdon, MD, Massachusetts General Hospital, Boston, MA; Katrina A. Gwinn-Hardy, MD, NINDS-NIH, Bethesda, MD; John Hardy, PhD, Laboratory of Neurogenetics, Bethesda, MD; Peter Heutink, PhD, VU University Medical Center, Amsterdam, The Netherlands; Howard Hurtig, MD, Pennsylvania Hospital of the University of Pennsylvania Health System, Philadelphia, PA; Takeshi Iwatsubo, MD, University of Tokyo, School of Pharmaceutical Science, Tokyo, Japan; Kenji Kosaka, MD, PhD, Yokohama City University School of Medicine, Yokohama City, Japan; Virginia Lee, PhD, University of Pennsylvania School of Medicine, Philadelphia, PA; Jim Leverenz, MD, Seattle, WA; Carol F. Lippa, MD, Drexel University College of Medicine, Philadelphia, PA; Eliezer Masliah, MD, University of California, San Diego, La Jolla, CA; Ian McKeith, F Med Sci., Newcastle University, Newcastle upon Tyne, UK; Robert L. Nussbaum, MD, Genetic Disease Research Branch, Bethesda, MD; C. Warren Olanow, MD, Mount Sinai Medical Center, New York, NY; Bernard M. Ravina, MD, University of Rochester School of Medicine, Rochester, NY; Andrew B. Singleton, MD, PhD, National Institutes of Health, Bethesda, MD; Caroline M. Tanner, MD, PhD, Parkinson's Institute, Sunnyvale, CA; John Q. Trojanowski, MD, PhD, University of Pennsylvania School of Medicine, Philadelphia, PA; Zbigniew K. Wszolek, MD, Mayo Clinical Jacksonville, Jacksonville, FL.

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