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Arguing Against the Proposed Definition Changes of PD

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ABSTRACT: As members of the Lewy Body Dementia Association Scientific Advisory Council, we aim to address some of the issues raised in the article titled “Time to Redefine PD? Introductory Statement of the MDS Task Force on the Definition of Parkinson’s Disease.” In particular, we suggest that the 1-year rule distinguishing Parkinson’s disease dementia from dementia with Lewy bodies is worth maintaining because it serves an important purpose in clinical practice and clinical and basic science research and when helping the lay community understand the complexity of these different clinical phenotypes. Furthermore, we

believe that adding an additional diagnostic label, “PD (dementia with Lewy bodies subtype),” will confuse rather than clarify the distinction between dementia with Lewy bodies and PD or PD dementia, and will not improve management or expedite therapeutic development. We present arguments supporting our contentions. © 2016 The Authors. Movement Disorders published by Wiley Periodicals, Inc. on behalf of International Parkinson and Movement Disorder Society.

Key Words: Dementia with Lewy bodies; dementia; Parkinson’s disease; parkinsonism

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We read with interest the article by Berg and colleagues¹ regarding possible changes to the definition of PD as proposed by the International Parkinson and Movement Disorders Society task force commissioned to consider a redefinition of PD. Comments were sought by the authors regarding the content of this article. We aim to address some of the issues raised in this article, particularly those relating to dementia and the distinction between dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD).

We agree that there is clinical overlap between DLB and PDD and concur that the 1-year time period may not be the optimal method for diagnostic distinction, but we also believe that the rule serves a useful purpose for clinical practice and research studies and that its dismissal would be both premature and problematic. We argue that insufficient new evidence has been presented to justify a modification to the diagnostic criteria for PDD and DLB at this time. We also believe that adding an additional diagnostic label, "PD (DLB subtype)," will confuse rather than clarify the situation and will not improve management or expedite therapeutic development.

Addressing the "Challenging the Status Quo" Comments

Relevant challenges to redefine PD from the manuscript are restated in italics below, with our responses stated beneath each challenge.

Similar neuropsychological findings, with predominant visuo-perceptual impairment, improvement of memory with cueing, and so on.

We concur that once the dementia is diagnosed, visual perceptual impairment, attention difficulty, and slowed reaction time occur in both DLB and PDD.^{2,3} However, the comorbid presence of Alzheimer's disease (AD) pathology is not uncommon in DLB and has been shown to contribute to greater verbal memory impairment.⁴ In addition, it is not known whether PDD and DLB differ cognitively in the predementia (ie, mild cognitive impairment [MCI]) stage, because the cognitive profile for the MCI of DLB has yet to be firmly established.⁵ One study found more severe cognitive deficits for patients in the MCI stage of DLB when compared with PD-MCI.⁶ These data raise questions about whether the early cognitive impairments of DLB and PDD are truly indistinguishable.

Similar nonmotor profile, with olfactory loss, depression, autonomic dysfunction, and sleep disorders in both.

Although these nonmotor features are indeed common to PD, PDD, and DLB, their frequency, phenomenology, prominence in the clinical picture, and timing and evolution may differ between PD, PDD, and DLB. Lumping nonmotor symptoms as part of the PD umbrella may deter further investigation into why these differences may emerge and what unique role they may play for DLB and other synucleinopathies.

Similar imaging, with overlapping patterns of cortical atrophy, glucose utilization, neurotransmitter changes, and diffusion tensor imaging.

As the authors acknowledged, amyloid deposition imaged with positron emission tomography is higher in DLB when compared with PD and PDD, and other group-level differences in neuroimaging parameters exist, including more gray matter atrophy on structural MRI in DLB when compared with PDD.^{7,8} These findings therefore underscore some key differences between DLB and PDD on imaging.

Similar prodromal stage: For example, patients with idiopathic RBD develop both syndromes, with little difference in clinical evolution patterns.

Rapid eye movement sleep behavior disorder (RBD) clearly can be an early manifestation of Lewy body disease, which eventually evolves into PD or DLB, and many patients with PD and DLB have features of RBD occurring years, or even decades, prior to the onset of parkinsonism cognitive or psychiatric features.⁹ The presence of RBD improves the diagnostic validity of the current DLB criteria.¹⁰ However, there is insufficient data to substantiate the claim that there is little difference in patterns of clinical evolution between DLB and PDD in those with a prodromal history of RBD.

Similar genetics: For example, family members with alpha-synuclein duplication or triplications as well as glucocerebrosidase (GBA) mutations can present with either condition.

Some of the most compelling evidence to maintain a distinction between PDD and DLB comes from recent studies that have uncovered some genetic differences between them. Specifically, single nucleotide polymorphisms in the gene encoding mitochondrial transcription factor A were found to be associated with PDD and not DLB.¹¹ Also, the apolipoprotein e E4 allele frequency was higher in pure DLB (ie, without concomitant AD pathology) than in PDD.¹² Furthermore, although GBA mutations are reported in both DLB and PD, pure DLB has an intermediate mutation frequency between AD and PD.¹³ A recent genomewide study of DLB also demonstrated different genetic risk factors when compared with PD.¹⁴

Addressing the "Defense of the Status Quo" Comments

Although patients with DLB and PDD look similar at end stage, the course can be extremely different.

The most agreed on and empirically demonstrated clinical difference between DLB and PDD pertains to clinical course in the context of the temporal onset of dementia and motor signs (ie, the 1-year rule). This has special relevance when considering the prodromal and preclinical stages of these neurodegenerative conditions. In these conditions, with both motor and cognitive deficits, when parkinsonian motor signs are the

initial clinical feature (PDD), the onset of dementia develops an average of 6 years later.^{15,16} When dementia is a presenting feature (as in DLB), the onset of parkinsonism develops an average of 2 years later.¹⁰ Clinical and pathologic differences are associated with a longer duration of parkinsonism relative to dementia onset and include older age,¹⁷ later onset of visual hallucinations,¹⁸ less severe cortical alpha-synuclein pathology, lower plaque scores, and greater cholinergic cortical deficits¹⁹ in PDD when compared with DLB. Also, there is a difference in severity as well as phenomenology of motor signs and response to dopaminergic therapy between the typical patient with PDD who has had many years of motor PD when compared with the archetypal patient who fits DLB criteria, whose duration of motor dysfunction is less, severity is often milder, and response to dopaminergic therapy is often less robust.

Many Parkinsonian DLB Patients Would Not Meet Criteria for Clinical PD

We agree with this statement and would add that in DLB there is also a subset of patients who do not have parkinsonism. These patients meet clinical criteria for probable DLB and have pathologic confirmation of Lewy body disease, but do not exhibit clear-cut extrapyramidal signs during life.¹⁰ This is one example of the phenotypic heterogeneity in DLB and an important reason why the most common misdiagnosis of DLB continues to be AD.²⁰ More work is needed to better understand DLB without parkinsonism, and placing DLB under the umbrella of PD may deter further investigation of the nonmotor and motor features of DLB.

Addressing the “Moving Forward” Comments

In the section titled “Moving Forward,” the authors suggest that we consider omitting the 1-year rule and propose using “PD (DLB subtype)” for those patients who meet clinical criteria for DLB and then fulfill criteria for PD while maintaining the diagnosis of DLB for those who never fulfill criteria for PD. We believe that there is insufficient evidence to support this change currently, and adding an additional diagnostic category will only confuse the distinction further.

We agree that the 1-year time period is arbitrary, may not be optimal, and will almost certainly be modified in the future when the genetic underpinnings, pathophysiologic mechanisms, and prodromal states of these disorders are better understood. It is well known that identifying a precise date of onset for either parkinsonism or dementia is often impossible, so that the difficulties posed by the hypothetical clinical scenario proposed by the authors, with onset of

dementia at 10 months, is likely rare in routine clinical practice and does not justify changing diagnostic criteria at this time. Empirical data are needed to determine whether the use of the 1-year cut-off has benefit, or if a longer cut-off between the onset of parkinsonism and the development of dementia would be a better demarcation of PDD from DLB. Although the 1-year rule may not be optimal, we argue that modifying the diagnosis of a DLB patient by whether they meet clinical criteria for PD would neither help patients and caregivers understand the prognosis nor serve to inform clinical practice, which was part of the original rationale for this guideline.^{21,22} To reliably distinguish parkinsonism from PD may be achievable in a specialist movement disorder setting, but would likely introduce significant variation across the wide range of different clinical settings in which dementia patients are assessed and diagnosed.

Implications for Diagnosis, Evaluation, Medical Management, and Social and Supportive Care

The diagnosis, evaluation, medical management, education, and community resources for patients with dementia and their families may be difficult to cover comprehensively when viewed from the perspective that PD (and thereby, by the task force’s implication, DLB) is predominantly a movement disorder. Clinical evaluation and the management of people with dementia raise complex issues and have to be delivered by a diversity of clinicians with very different levels of expertise.

Patients, families, and clinicians therefore require a diagnostic system that is simple, has high face validity, and is widely used. Two decades of concerted effort by the international research community has crafted a mutually agreed on approach to the diagnosis of PD, PDD, PD-MCI, and DLB, and modification of this approach should be clearly supported by empirical data. It is precisely this collaborative stability that has enabled both PDD and DLB to have entered *DSM-5*²³ and to have been assigned as a national research priority by the United States.²⁴

Summary and Recommendations

We argue that the statements from the 2005 Consensus Group on DLB continue to hold true.²² Therefore, we propose the following:

- The 1-year rule distinguishing PDD from DLB is worth maintaining because it serves an important purpose in clinical practice and clinical and basic science research and in helping the lay community understand the complexity of these apparently different clinical phenotypes. Modification of the

1-year time period may be justified when the genetic underpinnings, pathophysiologic mechanisms, and prodromal states of these disorders are better understood. Modifying the diagnosis of patients who meet diagnostic criteria for DLB based on whether they meet diagnostic criteria for PD is unjustified at this time, and the addition of a further diagnostic category, "PD (DLB subtype)," is not necessary and is potentially confusing.

- Continued attention should be given to identifying the mild or early manifestations of Lewy body disease and characterizing the longitudinal clinical and biomarker changes associated with evolving Lewy body disease.
- Symptomatic and disease-modifying interventions should be developed using pharmacologic and nonpharmacologic modalities for the syndromes associated with Lewy body disease.
- Both phenotypes should be included in clinical trials of new therapies for Lewy body dementia (as opposed to lumping them into 1 phenotype) until more research improves knowledge about the differences and similarities between PDD and DLB. ■

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