Dementia with Lewy Bodies and the Lewy Body Dementias: 2/1

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INTRODUCTION

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative cause of dementia in the Western world.[1] What had been presumed to be a rare disorder when first described,[2] turned out to be more common than expected. That Lewy bodies were found in the brains of 15–25% of cases that came to autopsy was a surprising discovery over 30 years later.[1] However, more recent clinical studies suggest that DLB makes up about 4% of community diagnoses of dementia.[3] While there are clinical criteria that distinguish DLB from Parkinson's disease with dementia (PDD), it is more accurate, as will be explained below, to lump the "Lewy body dementias" (LBD) together, unified both by their clinical signs and by their pathology.[4] PDD is far more common than DLB.

The Lewy body is a proteinaceous sphere (**Figure 1A,B**) found in the cytoplasm of occasional brain neurons, particularly in the brainstem-pigmented nuclei of these two neurodegenerative disorders, but is also found in the neuropil, outside of the cells, presumably a tombstone of a dead neuron. They are the hallmark pathological feature of both disorders required to make the diagnosis. The Lewy body was first described by Fritz Lewy, MD, in 1912. It is primarily composed of an abnormal variant of the protein, alpha-synuclein. While PD was first clinically described in detail in 1817 and was specifically noted by James Parkinson to spare cognition, DLB was first reported in a report by Stanley Aronson, MD, and his group in 1961,[2] with a novel finding of widespread cortical Lewy bodies in two adults with severe dementia and quadriplegia. Of note for this journal, Dr. Aronson, then a prominent neuropathologist in New York, became the founding dean of the medical school at Brown University and was a former Editor-in-Chief of the RIMJ for 10 years.

DEMENTIA WITH LEWY BODIES

The current clinical criteria for the diagnosis of DLB[4] is the fourth iteration since the first international symposium in 1996, and are contained in **Table 1**, unchanged since 2017.

Figure 1A. Lewy body in a substantial nigra cell, surrounded by neuro-melanin granules.

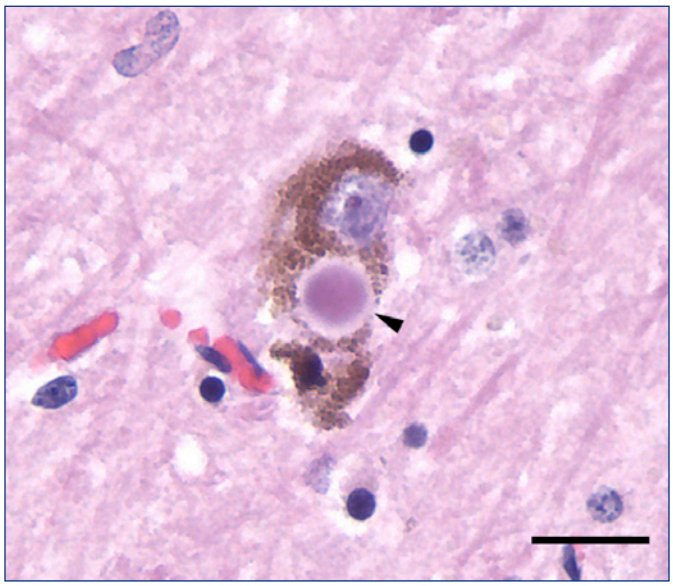
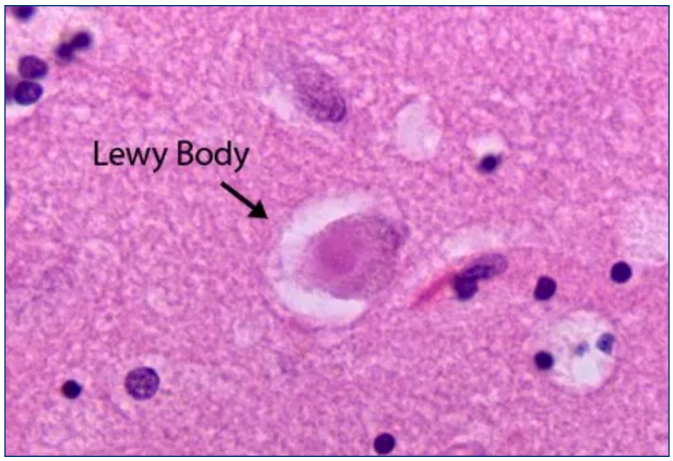


Figure 1B. Lewy body in the cortex.



Clinically, the disorder is often difficult to distinguish from Alzheimer's disease (AD) unless the patient has REM sleep behavior disorder or visual hallucinations, which are rare in AD. Memory disorders' experts miss the diagnosis about half the time when either of these two features are absent, because the other diagnostic criteria, while less common in

Table 1. 2017 Criteria for Dementia with Lewy bodies[4]

I. Required: dementia
II. Core clinical features: 2 required **a**. Fluctuating cognition, attention, alertness; visual hallucinations; REM sleep behavior disorder; parkinsonism
III. Supportive clinical features **a**. Neuroleptic sensitivity (parkinsonism); falls, imbalance; fainting or unresponsive spells; autonomic dysfunction; hyposmia; hypersomnia; non-visual hallucinations; delusions; apathy, anxiety, depression
IV. Indicative biomarkers
V. Abnormal DaT scan or MIBG myocardial scintigraphy; REM sleep w/o atonia
VI. Supportive biomarkers **a**. MR or PET imaging, EEG changes

AD, occur frequently enough to make diagnostic distinction impossible. Fluctuations in cognition or attention,[5] for example, are difficult to interpret and may also occur in AD. Many patients with dementing disorders have sleep disorders, often unrelated to the dementia, which predispose them to cognitive fluctuations due to daytime sleepiness. The vast majority are elderly and often take medications for hypertension, causing orthostatic hypotension, which may also cause cognitive fluctuations. Some parkinsonian features, such as motor slowness, stooped posture, reduced arm-swing, reduced spontaneous movements and imbalance are often part of what are often considered "usual" aging, previously labelled "senile-gait disorder,"[6] a term that has fallen out of favor. Episodes of reduced responsiveness are also not very helpful as AD patients may "tune out" as well, and frank coma is rare in DLB.[7] Although there are differences in the typical neuropsychological profiles of LBD and AD, they often overlap since there is overlap in the pathology in more than half the cases of the LBD, with neurofibrillary tangles being present, in addition to Lewy bodies. When visual hallucinations are present, the diagnosis of DLB is correct over 80% of the time.[8]

The typical cognitive profiles of the LBDs are: early deficits in attention, visual-spatial and executive function, without problems in language function or praxis.[8] These observations led to the commonly used comparison of "sub-cortical" vs "cortical dementias," based primarily on localization deduced from stroke and brain tumor cases. Language and praxis are considered cortical functions since their impairment are typically associated with pathology in the cortex, while executive function, involving planning and multitasking, are generally associated with subcortical or basal ganglia disorders. Early on, even prior to the development of dementia, PD patients decline on neuropsychological testing in these areas. Visual-spatial deficits occur in over 80% of DLB patients, so that its absence raises a red flag about a diagnosis.

In contrast, the typical neuropsychological changes that occur in AD involve language and praxis. The memory impairments are, in general different, too, in that LBD patients may form new memories but have difficulty retrieving them, whereas AD patients will most likely fail to lay down a memory trace at all. In addition, LBD patients are more likely to develop "neuropsychiatric" problems of anxiety, depression, fatigue and apathy early on, often preceding the development of the motor features of PD or even the memory and cognitive changes.

Although the "typical" neuropsychological patterns of the two disorders differ, there is often a significant overlap, which is most likely due to overlapping pathology. More than half of patients with LBD also have significant Alzheimer pathology, particularly neurofibrillary tangles, but also amyloid plaques, and many AD patients have Lewy bodies. What the connections between the two pathological processes are is unknown.[9]

PARKINSON'S DISEASE WITH DEMENTIA (PDD) AND THE TWELVE-MONTH RULE

Although James Parkinson in his famous monograph described the "senses and intellect being uninjured," this is, unfortunately, not usually the case after several years. The standard clinical criteria for diagnosing PD use dementia at onset as exclusionary, but dementia does develop in about 60–80% of PD patients, but usually several years after the onset of motor signs and symptoms. However, in some cases the dementia develops earlier. The guideline for distinguishing DLB from PDD is that if the dementia develops 12 months or more after the onset of motor symptoms, the diagnosis is PDD. If the dementia develops before the motor symptoms or within 12 months, then the diagnosis is DLB. It is often impossible to accurately make this distinction when first meeting a patient.

DIFFERENCES BETWEEN DLB AND PDD

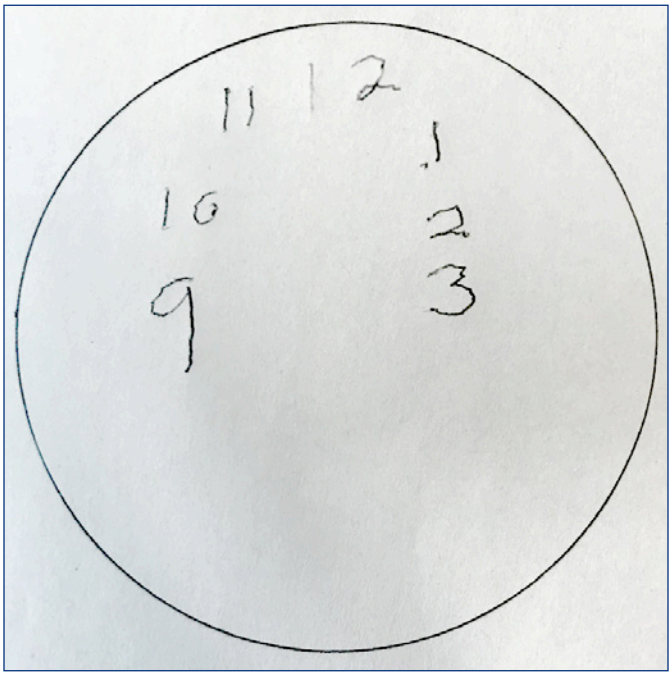
There are two clinical differences between these disorders. Most importantly, by definition, the dementia precedes or accompanies the motor features of PD within 12 months of motor onset. The second is the occurrence of visual hallucinations in DLB that are not associated with PD medication. In resource-wealthy regions, almost all hallucinatory experiences in PD are associated with the PD medications, but, on rare occasion, as in the case below, the hallucinations may occur without medication exposure. There have been no clear pathological differences between the two disorders, so that all authorities believe that the two disorders are very close, and some believe they are variants of the same disease, simply with the dementia beginning early.[10]

In general, DLB progresses more rapidly than AD, but the spectrum is wide.

CLINICAL EXAMPLE OF LBD

An 85-year-old man was evaluated for essential tremor (ET) and a gait abnormality. He had a stooped posture, reduced stride length, absent arm-swing, and mild slowness of movement. His tremor was typical of essential tremor, with no resting tremor. He was cognitively intact. His brain MRI showed a moderate degree of small vessel ischemic change. It was unclear if he had PD in addition to the ET, so a dopamine transporter (DaT) nuclear imaging scan was obtained and was normal. This was strong but not conclusive evidence against a diagnosis of PD. His parkinsonism was then ascribed to the white matter changes on MRI. He returned two years later with resting tremor, worsened bradykinesia, rigidity, and parkinsonian gait and dementia. In filling in a circle with numbers for a clock (see **Figure 2**), he had obvious problems completing the task, but also produced a large halo, particularly at the bottom, classic for PD, although the numbers were large. He also had developed occasional visual hallucinations, without being on any medications, as well as REM sleep behavior disorder.

Figure 2. Fill in the circle with numbers to make it look like a clock.



Because the dementia occurred more that 12 months after the parkinson motor features, he was diagnosed with idiopathic PD with dementia. Had the hallucinations and cognitive dysfunction been present a few months earlier, he would have met criteria for the diagnosis of DLB.

PATHOLOGY

The defining pathology of PD is the Lewy body, found in the pigmented brainstem nuclei locus coeruleus and the substantia nigra. In DLB, these are also seen, but with an increased number of these in the cortex and limbic system. These had not been seen in earlier years because of limited staining capabilities for histopathology. With increased sophistication, greater sensitivity for exposing LB has developed. In addition to the Lewy bodies in the brain, abnormal alpha-synuclein has been found to accumulate in neuronal processes and not just the cell body. These are even seen in peripheral nerves in the skin, which has led to a new diagnostic tool, the skin biopsy. A high percentage of DLB and PDD patients have amyloid plaques and neurofibrillary tangles sufficient to make a pathological diagnosis of concomitant AD.[9] When thinking about the two LBDs, one should keep in mind that the pathologies are identical and the neuropathologist can only make one or the other diagnosis based on the clinical history.

It is unfortunate that review articles on these disorders rarely note that pathologists are currently unable to estimate how many brain cells are lost in these disorders, what regions they are lost from, or what types of neurons they were. Thus, although much is known, we are largely dealing with "unknown unknowns" when we try to understand what goes wrong in the LBD. This will change soon, I believe, with automated techniques.

TREATMENT

As the two disorders are so similar, the treatments for their symptoms are identical as well. Although the cholinergic deficit in the LBD is greater than in AD, the cholinesterase inhibitors, three (donepezil, galantamine and rivastigmine) of the four FDA-approved medications for improving cognitive and memory function in mildly demented people, do not work any better than they do in AD. They are mildly helpful for memory and cognition, but not nearly as helpful for improving cognition or memory as L-Dopa is for mobility. They are mildly but not predictably helpful for reducing hallucinations in either of the LBDs, and have not been reported to improve delusions. The recently approved medications for AD reduce amyloid, which is thought to be important for AD, but is not directly involved in LBD and therefore not known to be useful in the LBD. Treating the parkinson features in DLB is, in most cases, limited to L-Dopa, the single most effective drug, which also has the least likelihood of causing or worsening hallucinations or delusions (and the least expensive). Treatment of motor problems is often limited by the mental side effects of L-Dopa, and, generally better postponed until the psychotic symptoms are controlled. Although no drug is FDA-approved for treating psychotic symptoms in DLB, pimavanserin is approved for this purpose in idiopathic PD. The strongest evidence in support of

an antipsychotic for psychotic symptoms in PD, for both demented and non-demented patients, is for clozapine, while quetiapine is, by far, the most commonly used. Quetiapine has been shown to not worsen motor problems in PD but has failed to show efficacy in three double-blind clinical trials.[11] Unfortunately, the other antipsychotic drugs have all been implicated in worsening motor function. Strong evidence earned olanzapine a Black Box warning for use in PD prior to all antipsychotics being labelled with this stigma. Less strong evidence exists for the dangers of aripiprazole and risperidone. Once psychotic symptoms are controlled, low dose L-Dopa is recommended, with close observation.

COMMENTS

PD is a common disorder, affecting about 1% of Americans over the age of 60. The majority of PD patients, but not all, develop dementia. The variety of clinical signs, their speed and order of progression, have prompted many experts to opine that PD is actually a collection of related diseases.[12] Using this hypothesis as a model, this author believes it makes more sense to consider DLB as one of these in which dementia occurs early, rather than that they are distinct diseases.

It is important to understand that neither the causes of these disorders nor their full pathologies are understood. Many gene abnormalities have been implicated in both sets of disorders. In PD, with the exception of alpha synuclein gene abnormalities, no single gene carries more than a 10% likelihood of producing PD. Furthermore, although Lewy bodies form the identifiable marker of the disease, with a loss of cells in certain locations, this does not account for the shrinkage seen in PDD brains. There have been cases of familial PD in which some affected members, although clinically identical, had LB and others did not, raising obvious questions about the importance of the LB. AD also has variants, the most obvious being the cortico-basal syndrome and the posterior-cortical variant, which are clinically very different than our usual conceptualization of AD.

CONCLUSION

PDD and DLB are disorders that are probably different points on the same spectrum. They are clinically and pathologically indistinguishable, differing only as to when the dementia begins with regards to the motor impairments. Our treatments are symptomatic only, and, unlike the situation with AD, not at a stage where we have reasonable interventions that may reverse disease or slow progression.

References

1. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathological diagnosis of dementia with Lewy bodies: report of the consortium on dementia with Lewy bodies international workshop. Neurology. 1996;47:1113-24.
2. Okasaki H, Lipkin LE, Aronson SM. Diffuse intracytoplasmic ganglionic inclusions (Lewy type) associated with progressive dementia and quadriparesis in flexion. J Neuropathol Exp Neurol. 1961;20:237-443.
3. Vann Jones SA, O'Brien JT. The prevalence and incidence of dementia with Lewy bodies: a systematic review of population and clinical studies. Psychol Med. 2014;44:673-683.
4. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB consortium. Neurology. 2017;89:88-100.
5. Matar E, Shine JM, Halliday GM, Lewis WJG. Cognitive fluctuations in Lewy body dementia: towards a pathophysiological framework. Brain. 2020;143(1):31-46.
6. Elble RJ, Hughes L, Higgins C. The syndrome of senile gait. J Neurol. 1992;239(2):71-75.
7. Friedman JH. Episodic coma in Lewy body disorders: An observational report. Neurohospitalist. 2024 Sep 18:19418744241286579. doi: 10.1177/19418744241286579
8. Busse C, Mitolo M, Mozzetta S, et al. Impact of Dementia with Lewy body disease on visual skills and memory ability. Front Psychiatry. 2024 Dec 10;15:1461620. doi 10.3389/fpsyt.2024.1461620
9. Jellinger KA. Pathobiology of cognitive impairment in Parkinson's disease: Challenges and outlook. Int J Mol Sci. 2023;25(1):498.
10. Borghammer P, Okkels N, Weintraub D. Parkinson's disease and dementia with Lewy bodies: one and the same. J Parkinsons Dis. 2024;14:383–397.
11. Friedman JH. Pharmacological interventions for Parkinson's disease psychosis. Exp Opin Pharmacother. 2018;19(5):499-505.
12. Weiner WJ. There is no Parkinson disease. Arch Neurol. 2008;65(6):705-708.

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