Diagnosis and Management of Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB) is a disorder with a mixture of complex cognitive, psychiatric and neurological features that can be challenging for patients, caregivers and clinicians alike. Considered to be the second-most common neurodegenerative dementia, DLB is an important diagnosis for clinicians to make and to treat. This article will review the pathological and clinical features of DLB, as well as discuss its management.

by Ron Keren, MD, Psy, FRCPC

It took a long time from the first descriptions of Parkinson’s disease (PD) in 1817, to appreciate that the same Lewy bodies, identified for many years in the brainstems of patients with PD, could be a leading cause of dementia when found more diffusely in the cortex. First described by Friederich Lewy in 1912,¹ these intracytoplasmic inclusion bodies were long known as the histopathological hallmarks of PD. Interestingly, James Parkinson, who first described the illness that bears his name, believed that cognitive decline was not a part of PD.² In 1923, almost a century later, Friederich H. Lewy reported on 54 of 70 PD patients with considerable mental disturbances, but did not discuss a cause.³ In 1933, in his textbook, Diseases of the Nervous System,⁴ Brain reported that while PD patients do not necessarily experience cognitive decline, those patients who have a more diffuse pathological process, involving other parts of the brain might experience dementia. Finally, in 1961, Okazaki et al⁵ described two patients with dementia associated with behavioral and motor disturbances that had inclusion bodies in the cerebral cortex, indistinguishable from the Lewy bodies seen in PD.

Poorly visualized in the cortex with traditional staining techniques, reports of cortical Lewy bodies were rare until the 1970s, when the development of new staining techniques for the protein ubiquitin led to the establishment of cortical Lewy bodies as a cause of dementia. In 1989, Gibb stated “… Lewy bodies in the cerebral cortex may be associated with dementia more frequently than recognized.”⁶ Since then, a number of different terms describing the cognitive decline caused by Lewy bodies were coined, many of them depicting on a relationship between Lewy body and Alzheimer pathology. Terms such as the Lewy body variant of Alzheimer’s disease...
(AD), AD with incidental Lewy bodies, and AD with PD changes, suggested that AD was the predominant pathology, while terms such as senile dementia of the Lewy body type, cortical Lewy body dementia, dementia with cerebral Lewy bodies and diffused Lewy body disease implied that cortical Lewy bodies were the predominant pathology.

In 1996, an international consortium established the term “dementia with Lewy bodies” (DLB) and developed consensus guidelines for its clinical and pathological diagnosis. Today, DLB is generally accepted as the second-most common cause of neurodegenerative dementia in older people.

The Synucleinopathies and Lewy Body Disorders
A-synuclein is a normal synaptic protein that has been implicated in vesicle production. The synucleinopathies are a subset of neurodegenerative disorders that share a common pathology where insoluble fibrillary aggregates of a-synuclein can accumulate in both neurons and glia. In Lewy body disorders (DLB and PD), the aggregates accumulate in Lewy bodies. In multiple system atrophy (MSA), aggregates are found in glial cytoplasmic inclusions. In addition to a-synuclein, Lewy bodies are composed of neurofilaments, crystallin and ubiquitin. Antibodies to a-synuclein used to immunostain Lewy bodies have helped to better visualize Lewy body pathology.

PDD and DLB
Parkinson’s disease dementia (PDD) and DLB share overlapping clinical symptoms and neuropathology. Patients with PD who live long enough are likely to develop PDD (Figure 1). Longitudinal studies of patients with PD show that 78% of patients meet DSM IIIIR criteria for dementia after an average of a decade of motor symptoms. Most of these patients have fluctuating cognition and visual hallucinations similar to DLB, as well as extensive cortical Lewy bodies at autopsy. However, while validated diagnostic criteria have been established for DLB, there are no such diagnostic criteria for PDD, nor are there definite pathological criteria that differentiate between the two. The consensus guidelines for DLB set an arbitrary “one-year rule” to separate DLB from PDD. Onset of dementia within 12 months of parkinsonism qualifies as PDD. Given that PDD and DLB are likely different representations of the same underlying pathology, it has become increasingly accepted that they are more likely two points on a spectrum of a disease rather than two separate diseases, as suggested by the consensus guidelines.

DLB with AD Pathology
The pathological diagnosis of DLB does not exclude the presence of plaques and tangles as seen in AD pathology. In fact, most patients with DLB also have AD pathology. The degree of AD pathology, especially neurofibrillary tangles, affects the clinical presentation of DLB and may help explain why DLB is often clinically unrecognized. In a review by Merdes et al, 89 of 98 patients (91%) with autopsy-proven DLB met the criteria for AD set out by the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD). Patients with a low burden of AD tangle pathology (n = 24) were
much more likely to have visual hallucinations (66%) than patients with a high burden of AD tangle pathology (33%, n = 66). Similarly, the clinical diagnostic accuracy for DLB was higher in subjects with low tangle burden (75%) than those with high tangle burden (39%). The study concludes that the degree of concomitant AD tangle pathology has an important influence on the clinical features of DLB as well as its diagnostic accuracy.

The Clinical Diagnosis of DLB
In 1996, an international meeting was held to develop the consensus criteria for the diagnosis of DLB. In addition to the central feature of dementia, CERAD described three core clinical features of DLB: recurrent visual hallucinations, fluctuating cognition and spontaneous motor features of parkinsonism. A diagnosis of probable DLB requires the presence of two core features, while the diagnosis of possible DLB requires the presence of one core feature. CERAD also described a number of clinical features that support a diagnosis of DLB, including: repeated falls, syncope, transient loss of consciousness, neuroleptic sensitivity, systematized delusions, and hallucinations in other modalities. In 1999, a second consensus conference was held and added sleep behavior disorder and depression to this list. A history of stroke or any other physical illness or brain disorder sufficient to interfere with cognitive performance would make a diagnosis of DLB less likely (Figure 2). Using these criteria, the specificity of diagnosing DLB is quite high. However, the sensitivity is generally low, suggesting that the diagnosis can easily be missed using the consensus criteria (Table 1). McKeith et al suggest that diagnostic accuracy may be improved by the use of standardized methods for identifying fluctuation and through measuring medial temporal lobe atrophy on MRI, which is significantly less in DLB than in AD. Also, reduced dopamine transporter activity in the striatum, visualized by FP-CIT-SPECT in DLB, but not in AD.

Clinical Features of DLB
Age of onset ranges from 50 to 83 years, slightly favoring males. Mean survival time is similar to AD. However, some patients run a more aggressive course, progressing to death within one to two years from the onset of symptoms. The clinical features of DLB can be divided into three categories: cognitive, psychiatric and neurological.

Cognitive features. A decline in cognitive function is almost always the presenting feature of DLB. Many studies have looked at the neuropsychological features that may help distinguish between the cognitive decline in DLB and that in AD. A systematic review and meta-analysis completed by
Collerton et al.\textsuperscript{14} concluded that DLB might be conceptualized as a visual-perceptual and attentional-executive dementia. Shimomura et al.\textsuperscript{15} described a disproportionate impairment of visuoperceptual and visuoconstructive ability with relative sparing of memory function in DLB. For clinical purposes, early impairments in the drawing of the intersecting pentagons in contrast to performance on tests of short-term memory may be helpful in distinguishing DLB and AD patients.\textsuperscript{16}

Fluctuations in cognitive function can vary over minutes, hours or days, and occur in 50\% to 75\% of patients.\textsuperscript{12} Fluctuations are not exclusively found in DLB. However, compared to those found in AD, the amplitude of fluctuations in DLB appear to be more marked. Fluctuating cognition in DLB has been described as having a spontaneous, periodic, transient quality, appearing to be an interruption in the ongoing flow of awareness or attention.\textsuperscript{17} The gold standard for determining fluctuation is “expert opinion” which has low inter-rater reliability.\textsuperscript{18} Resulting from this, fluctuations in cognitive function may be the most difficult of the three core features for clinicians to characterize, likely contributing to the low sensitivity in diagnosing DLB, using the current criteria. The use of questionnaires and diary-keeping by a reliable informant and the use of specific psychometric procedures, including computer-based tasks that are sensitive to attention, were recommended in the report of the second DLB workshop.\textsuperscript{12} Ferman et al.\textsuperscript{19} developed a 19-item Fluctuations Composite Scale. The four distinguishing features of this scale that differentiate between patients with DLB and AD were daytime drowsiness and lethargy, daytime sleep lasting at least two hours, staring into space for long periods, and episodes of disorganized speed. Three or four of these features were present in 63\% of patients with DLB and in 12\% of patients with AD, resulting in a positive predictive value of 83\% for the diagnosis of DLB.

**Psychiatric features.** Early and prominent psychiatric features, especially vivid visual hallucinations, but also delusions, apathy and anxiety, occur early in the course of DLB. They tend to persist and help differentiate between DLB and other dementias (Table 2). Approximately two-thirds of patients report vivid, colorful and complex visual hallucinations of mute images, often of people or animals, similar to those reported in PDD. Individuals may respond to their hallucinations with amusement, apathy or intense fear.\textsuperscript{13} The presence of visual or auditory hallucinations in patients with Mini-Mental State Examination scores greater than 20 were found to be even more suggestive of DLB.\textsuperscript{20} Evidence from the psychopathology literature suggests that hallucinations are linked to a problem with reality monitoring\textsuperscript{21} which may lead to confusion between self-generated mental images and perception.\textsuperscript{22} Delusional misidentification has been found to be common in DLB.\textsuperscript{20} Depression has been found to be frequent in both DLB and PDD and may be linked to the severity of motor symptoms.\textsuperscript{20} A better understanding of the mechanisms underlying the various neuropsychiatric features of DLB will help in developing safe and effective treatments.

**Neurological features.** Up to 70\% of patients have parkinsonism, with bradykinesia, limb rigidity and gait disorder being the most common features.\textsuperscript{23} Extrapyramidal signs are seen in 25\% to 50\% of

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mega et al</td>
<td>75%</td>
<td>79%</td>
</tr>
<tr>
<td>Holmes et al</td>
<td>22%</td>
<td>100%</td>
</tr>
<tr>
<td>Luis et al</td>
<td>57%</td>
<td>90%</td>
</tr>
<tr>
<td>Verghese et al</td>
<td>61%</td>
<td>84%</td>
</tr>
<tr>
<td>McKeith et al</td>
<td>83%</td>
<td>95%</td>
</tr>
<tr>
<td>Lopez et al</td>
<td>23%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 1

Sensitivity and Specificity Using Clinical Consensus Criteria for Probable DLB\textsuperscript{13}
patients at the time of diagnosis and while most patients will develop some motor features during the course of the disease, up to 25% may not.23 Patients with DLB are thought to show greater postural instability and facial impassivity, with a tendency towards less tremor.13 In a prospective clinico-pathological study, the absence of extrapyramidal signs was the most common reason for missing the diagnosis of DLB.24 The rate of progression of motor symptoms in DLB is similar to that of PD.

RBD and DLB

Rapid-eye movement (REM) sleep behavior disorder (RBD) is parasomnia characterized by loss of normal skeletal muscle atonia during REM sleep, resulting in vivid and frightening dreams with simple or complex motor behavior.13,25 It has been associated with DLB, PD, progressive supranuclear palsy (PSP) and MSA, but not with AD or frontotemporal dementia.25 RBD may predate the development of parkinsonism or dementia in patients with DLB, PD or MSA by years or even decades.25 The association between RBD and DLB is so strong, with a high specificity, that Boeve et al26 suggest that it be added to the core features of DLB.

Autonomic Dysfunction in DLB

Autonomic abnormalities are more common in patients with DLB than in those with AD or in age-matched controls.13 In a cohort of 30 patients with DLB and 35 patients with AD, 77% of the DLB patients and 55% of the AD patients were found to have some form of neurovascular instability, such as orthostatic hypotension or carotid-sinus hypersensitivity.27 In a clinicopathologic cohort of 29 patients with DLB, all but one patient displayed some form of dysautonomia. Urinary incontinence was the most frequent (97%) symptom, with constipation occurring the second-most frequently (83%). Episodic hypotension and urinary retention occurred in 28%, hypertension without syncope in 66% and slightly elevated temperature in 72%.28

Neuroleptic Sensitivity

All older patients are susceptible to the extrapyramidal side effects of neuroleptics. Patients with DLB have been found to be especially sensitive to these agents, including atypical neuroleptics. McKeith et al29 reported that 50% of DLB patients exposed to neuroleptics experienced a severe sensitivity reaction which included cognitive decline, parkinsonism, drowsiness, and features of the neuroleptic malignant syndrome (NMS): with a three-fold increase in mortality. These reactions were not dose-related. Similarly, Ballard et al30 reported severe sensitivity reactions to neuroleptics in 29% of patients.
Differential Diagnosis
The main differential diagnoses are AD, vascular dementia, PDD, PSP, MSA, corticobasal degeneration and prion disease.13

Management
Barber et al32 describe a four-step approach to the management of DLB: establishing an accurate and timely diagnosis, identification of the severity and nature of key problem symptoms (cognitive, psychiatric and motor, including their effect on caregivers), nonpharmacologic interventions and pharmacologic interventions.

Nonpharmacologic interventions have not been systematically reviewed. However, given the limitations of pharmacologic treatments, they are the mainstay of clinical management. Educating patients and their caregivers about the nature of the disorder and assisting with coping strategies can be helpful. Motor impairments may benefit from mobility aids and physiotherapy.32

ChEIs. Given the profound cholinergic deficits in the cortex, brain stem and basal forebrain nuclei, in addition to the relative sparing of post-synaptic cortical muscarinic receptors, treatment with cholinergic agents would seem to benefit patients with DLB. Indeed, open-label studies with cholinesterase inhibitors (ChEIs; donepezil, rivastigmine and galantamine) suggest a clinical benefit in cognitive and behavioral domains.33-36 In a case report of nine patients with DLB treated with donepezil, there was an improvement in hallucinations in eight patients. However, there was a worsening of motor symptoms in three patients.37

A multi-centre, randomized, controlled trial of rivastigmine38 supported the findings of open-label studies, showing benefits in cognitive and behavioral outcomes. Rivastigmine significantly reduced the core psychiatric symptoms of DLB (apathy, anxiety, delusions and hallucinations). Twice as many patients on rivastigmine as on placebo were clinical responders, defined as having at least a 30% improvement from baseline with regard to behavioral symptoms. Rivastigmine also had a beneficial effect on fluctuations in attention as assessed using computerized choice reaction time tasks.39 There was no worsening of motor symptoms, and safety and tolerability were judged acceptable.

Despite limited evidence in randomized, controlled trials, and because of the risk of severe sensitivity reactions to neuroleptics, ChEIs are viewed by some to be first-line treatment for both the cognitive and psychiatric symptoms of DLB. However, in addition to the known gastrointestinal side effects associated with this class of drugs, clinicians should be aware of the potential for worsening of motor and autonomic symptoms. Clearly, more randomized, controlled trials are needed to further establish both the efficacy and safety of these drugs in the treatment of DLB.

Other Medications
Evidence for the treatment of Parkinsonism is limited. The effectiveness of levodopa (L-dopa) on motor symptoms in DLB has not been established but is probably less than in PD.13 L-dopa has the potential to exacerbate hallucinations in patients with DLB, challenging the clinician to balance between increased function and worsening psychosis.

Both clonazepam and melatonin have been suggested for the treatment of REM sleep behavior disorder.40

All older patients are susceptible to the extrapyramidal side effects of neuroleptics. Patients with DLB have been found to be especially sensitive to these agents, including atypical neuroleptics.
References: