

DEMENTIA WITH LEWY BODIES

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ABSTRACT

Dementia with Lewy bodies (DLB) took many years to crystallize into a recognizable clinico-pathologic entity. Neuropathologic findings of α -synuclein lesions in Lewy bodies and neurites correspond to dysfunction of the substantia nigra, and lesions in subcortical, limbic, and cortical regions are associated with cognitive, neuropsychiatric, and motor manifestations, which may be modified by coexisting Alzheimer tangle pathology. Clinical diagnostic criteria combining cognitive decline with features of parkinsonism, fluctuation of cognition, and visual hallucinations have been revised several times. The latest revision recognizes the importance of REM sleep behavior disorder as a clinical feature and bridges DLB and Parkinson's disease with dementia by removing an arbitrary 1-year separation between onset of motor and cognitive symptoms. Neuropathologic diagnosis now assigns a weight to both α -synuclein and Alzheimer's disease lesions. Treatment remains symptomatic and usually requires sensitive manipulation of a combination of medications to try to stabilize or improve cognitive, behavioral, and motor symptoms while minimizing side effects.

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BACKGROUND: A BRIEF HISTORY OF LEWY BODIES AND DEMENTIA

Friedrich Lewy described the cytoplasmic inclusions that bear his name in a 1923 publication on a series of patients with parkinsonism, of whom almost 50% were demented. This contrasted with James Parkinson's description of "the shaking palsy" in which the intellect and senses were spared. Over the next 50 years, there were only sporadic descriptions of Lewy body-associated dementia, but this changed in the 1980s when Kosaka described a series of patients with dementia and neuropathology of cortical Lewy bodies. Since then, research has burgeoned, and research centers worldwide have documented cortical Lewy bodies in elderly patients with dementia. Lewy bodies are found in limbic or cortical regions in about 20% of

patients with dementia, and amygdala-restricted Lewy bodies in another 20% to 30%. Dementia with Lewy bodies is now viewed as the second most common form of degenerative dementia after Alzheimer's disease (AD). Neuropathologic tools have improved, and ubiquitin immunostaining, used in the 1980s, has been supplanted by immunostaining with antibodies to α -synuclein. This allows easy identification of cortical Lewy bodies and abundant α -synuclein-positive neurites in affected brain regions.

In clinico-pathologic correlation studies of dementia with Lewy bodies, AD pathology often coexisted. Investigators gave the syndrome different names, including Lewy body dementia, senile dementia of the Lewy body type, diffuse Lewy body disease, and Lewy body variant of AD. At a consensus workshop in 1995, clinical and

KEY POINTS:

- Dementia with Lewy bodies is the second most common degenerative dementia in the elderly.
- The defining neuropathology of dementia with Lewy bodies is α -synuclein aggregation to form Lewy bodies and neurites.

KEY POINTS:

- α -Synuclein pathology is often diffuse and widespread in dementia with Lewy bodies, spreading beyond the brain stem to involve limbic and neocortical regions.
- Alzheimer pathology, particularly amyloid deposition, often accompanies dementia with Lewy bodies.

neuropathologic criteria were proposed and the entity received the neutral name of dementia with Lewy bodies (DLB), which acknowledges association but not causality (McKeith et al, 1996). The clinical description focused on patients in whom dementia either preceded parkinsonism or began no later than 12 months after the onset of Parkinson's disease (PD). Core clinical elements of DLB were dementia with prominent visuoconstructive and frontal-subcortical impairment, fluctuating levels of alertness and cognition, neurobehavioral symptoms of visual hallucinations, and parkinsonian signs. The next stage was to evaluate these criteria against neuropathology in patients followed to autopsy. Several studies found that the DLB criteria had high specificity but variable, though usually low, sensitivity. Therefore, refinements were proposed, including careful delineation of when in the time course core symptoms developed, better ways to assess fluctuation, and consideration of additional core symptoms. At the same time, neuropathology insights emerged. α -Synuclein pathology is associated with aging, with a frequency in nondemented elderly persons that may exceed 10% (Bennett et al, 2006). Lewy bodies restricted to the amygdala have been found commonly in AD and other neurodegenerative disorders (Hamilton, 2000) but are far less likely to be associated with clinical manifestations than Lewy bodies found in the limbic cortex or neocortex. Recent clinico-pathologic studies have shown that patients with substantial AD tangle pathology are less likely to show clinical features of coexisting Lewy body pathology, and the clearest DLB clinical phenotype occurs in those patients with relatively few tangles (Merdes et al, 2003). A biological relationship may exist between amyloid deposition and Lewy body formation. For exam-

ple, at least 30% of patients with early-onset familial AD have Lewy bodies in addition to AD pathology (Snider et al, 2005). In later-life DLB, biochemical analysis has shown that the amount and distribution of insoluble amyloid β -protein (A β 42) is comparable with that in AD (Deramecourt et al, 2006). The proposed neuropathologic assessment and classification of DLB now includes staging of AD tangle pathology as well as α -synuclein pathology, and the relative amounts of each of these lesions is used to determine whether the clinical phenotype of DLB had high, low, or intermediate probability (McKeith et al, 2005).

As clinicians have increasingly focused on nonmotor features of PD, it is now appreciated that subtle changes in neuropsychological performance occur in many patients. People with PD are at risk for dementia, which may develop in 20% to 30% and is associated with age and duration of symptoms (reviewed in Emre, 2003). The neuropathology underlying PD with dementia (PDD) varies: although some patients show AD pathology and others have vascular lesions, the most common finding is diffuse α -synuclein pathology affecting cortical regions. Braak and colleagues (2003) proposed a staging system for α -synuclein pathology in PD in which lesions spread from subcortical areas, such as the reticular activating system, to the locus ceruleus and substantia nigra, then to hippocampal regions, and finally to the neocortex. Because the neuropathology of a patient with PDD may be identical to that of DLB, the important question of whether to keep boundaries between these disorders or unite them under an umbrella of Lewy body disease is being debated. Recent studies have found many clinical similarities between DLB and PDD, including profiles of cognitive impairment (Aarsland et al, 2004; Janvin et al, 2006) and

degree of responsiveness to acetylcholinesterase inhibitors (Thomas et al, 2005). With greater clinical and research experience of DLB and PDD, changes to the DLB criteria were recently proposed, allowing PDD and DLB to be considered as a single entity for certain types of studies.

CLINICAL ASSESSMENT AND DIAGNOSIS OF DEMENTIA WITH LEWY BODIES AND RELATED DISORDERS

The recently revised clinical diagnostic criteria for DLB are presented in **Table 3-1**. Before discussing how to apply these diagnostic criteria, it is helpful to review the clinical features of DLB. These features can be conveniently classified in domains or systems, which form a useful framework for comprehensively evaluating patients in the clinic. The domains are cognitive impairment, neurobehavioral/psychiatric symptoms, parkinsonism, disorders of sleep, and autonomic impairment. Although the revised DLB diagnostic criteria incorporate the use of imaging tests to visualize the dopaminergic system, the history and examination remain pivotal in making the diagnosis.

Cognitive Symptoms

Cognitive symptoms usually have a gradual onset and progression. A prominent feature is fluctuation, which may refer to episodes of decreased attention, staring spells, or confusion, which may last from seconds to hours. Fluctuation may be difficult to identify in DLB, but when present, the history will often be striking and dramatic, unlike AD where patients may have good days and bad days. Because of the difficulty identifying fluctuation, rating scales have been developed. Having an informant keep a diary, a brief fluctuation questionnaire (Walker et al, 2000), and psychometric tests that

measure variability in choice reaction time have been proposed as indices of fluctuation in DLB. A brief set of questions about daytime drowsiness, sleeping 2 hours or more per day, staring into space, or episodes of disorganized speech have pointed to DLB rather than AD (Ferman et al, 2004). These structured approaches require further study; otherwise fluctuation will remain a subjective and very difficult criterion.

Cognitive symptoms in DLB include forgetfulness; impaired judgment, organization, and planning; getting lost; and trouble with spatial perception. Decreased initiation is often a prominent feature, although this can also be found in AD. Some patients exhibit striking visuospatial impairment with symptoms such as difficulty navigating around their homes or even difficulty trying to sit down in a chair. Formal psychometric testing can reveal a profile, particularly early in the course of dementia, of relatively severe impairment on frontal-subcortical (executive) tasks as well as visuospatial tasks. This pattern may be difficult to detect with brief tests such as the Mini-Mental State Examination (MMSE). However, a simple office test such as clock drawing, particularly asking the patient to copy a clock, can reveal the visuospatial deficits in DLB even at a mild stage. Standard psychometric tests show these deficits more clearly, and a number of studies have demonstrated that the cognitive profile of DLB may differ from that of AD, particularly at mild to moderate stages of dementia (Collerton et al, 2003). Although both disorders share the feature of impairment of episodic memory, DLB often shows worse performance on tests of psychomotor or executive function, or visuoconstructive or perceptual tests. Several studies have reported a similar profile of selective cognitive impairment in PDD

KEY POINT:

- To distinguish dementia with Lewy bodies from Alzheimer's disease, look for fluctuations of alertness or cognitive performance, visual hallucinations, and parkinsonism relatively early in the clinical course of dementia.

TABLE 3-1 Revised Criteria for the Clinical Diagnosis of Dementia with Lewy Bodies▶ **Central Feature (Essential for Diagnosis)**

Dementia with progressive cognitive decline of sufficient magnitude to interfere with social or occupational function. Memory impairment may not necessarily occur early but usually develops with progression. Deficits on tests of attention, executive function, and visuospatial ability may be prominent.

▶ **Core Features (Two or More Core Features = Probable DLB, One = Possible DLB)**

Fluctuating cognition—pronounced variation in attention and alertness

Recurrent visual hallucinations, typically well formed and detailed

Spontaneous parkinsonism

▶ **Suggestive Features (One Core Feature Plus One Suggestive Feature = Probable DLB; Zero Core Features Plus One or More Suggestive Feature = Possible DLB)**

REM sleep behavior disorder

Severe neuroleptic sensitivity

SPECT or PET imaging showing low dopamine transporter activity in basal ganglia

▶ **Supportive Features**

Repeated falls and syncope

Transient, unexplained loss of consciousness

Autonomic dysfunction

Other types of hallucinations

Systematized delusions

Depression

Relatively preserved medial temporal lobe structures on CT/MRI

Low uptake on SPECT diffusion scan with decreased occipital activity

Low uptake of metaiodobenzylguanidine myocardial scintigraphy

Prominent slow-wave activity on EEG, with temporal lobe transient sharp waves

▶ **A Diagnosis of DLB Is Less Likely**

In the presence of stroke evident as focal neurologic signs or on brain imaging

In the presence of other physical illness or brain disorder that can account in part or in total for the clinical picture

If parkinsonism only appears first at a stage of severe dementia

▶ **Temporal Sequence of Symptoms**

DLB is diagnosed when dementia precedes or is concurrent with parkinsonism. Parkinson's disease dementia should be used to describe dementia that occurs in the context of well-established Parkinson's disease. For research studies that distinguish between DLB and Parkinson's disease with dementia, the 1-year rule that dementia should begin no later than 1 year after onset of parkinsonism for a diagnosis of DLB is recommended.

DLB = dementia with Lewy bodies.

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and DLB (Aarsland et al, 2003; Ballard et al, 2002).

Although memory decline may not be prominent initially in DLB, many studies show that memory performance is equally impaired in AD and DLB patients matched for level of dementia. The rate of progression of decline in cognition overlaps in AD and DLB. However, some patients with DLB may decline much more rapidly, and case reports have documented patients with extremely rapid progression. In earlier case series, rapid decline could sometimes be attributed to neuroleptic sensitivity. Typical neuroleptics are now avoided in DLB, but patients with rapid progression are still seen, suggesting that intrinsic neuropathology may sometimes spread or develop rapidly for poorly understood reasons.

Parkinsonism

Parkinsonism varies in DLB and may be more subtle than that found in idiopathic PD. Many studies have noted a preponderance for axial signs, including gait difficulty and postural instability, with less common rest tremor, which resembles the postural instability gait disorder subtype of PD that is more likely to develop cognitive impairment (Burn et al, 2006). However, some patients may show more florid parkinsonism. The detailed assessment of parkinsonism in demented patients is difficult because cognitive impairment and apraxia may make it difficult for patients to follow instructions to perform motor tasks. Studies have suggested that certain items within the Unified Parkinson's Disease Rating Scale are more reliable in dementia, namely rest tremor, action tremor, body bradykinesia, facial expression, and rigidity. However, assessments of gait and postural instability are an important component of the examination because regardless of diagnostic

specificity, they have implications for patients' mobility and risk of falls. Patients with DLB are less likely to show a good or prolonged response to levodopa than those with PD or PDD, but a trial of treatment is warranted (Molloy et al, 2005). This may be explained by more widespread pathology in DLB that directly affects the striatum, as well as by deficits in nondopamine neurotransmitter pathways.

Patients with DLB are predisposed to falling for a number of reasons, including parkinsonism, impaired postural (righting) reflexes, and autonomic impairment, as well as general problems such as aging, deconditioning due to lack of activity, and dementia.

Behavioral/Neuropsychiatric Symptoms

Recurrent, complex visual hallucinations are one of the most helpful features in DLB. Patients typically report seeing people, animals, or insects and can sometimes describe them in great detail (McKeith et al, 1996). DLB patients with visual hallucinations have more severe visuospatial dysfunction than those without. In PDD, visual hallucinations may be precipitated or worsened after treatment with levodopa or dopamine agonists. However, studies have found that in PD, hallucinations sometimes persist even after these medications are decreased in dose and may be a predictor of dementia, linking PDD with DLB. The anatomical basis of hallucinations is not clear. Disturbances in integrative visual pathways may result from Lewy bodies in the inferior temporal lobe, while other possibilities include relatively severe cholinergic deficits in the temporal lobe. Occipital lobe hypometabolism on PET scanning may be a marker of DLB and can distinguish DLB from AD. However, the sensitivity of this finding for DLB is not clear because studies

KEY POINTS:

- Dementia with Lewy bodies and Alzheimer's disease share the gradual onset of dementia with forgetfulness.
- The clinical response to levodopa is often less dramatic in dementia with Lewy bodies than in idiopathic Parkinson's disease.
- Formed visual hallucinations, often consisting of images of people, animals, or insects, are common in dementia with Lewy bodies.

KEY POINTS:

- REM sleep behavior disorder, in which patients appear to act out their dreams, is common in dementia with Lewy bodies and can precede dementia.
- Autonomic symptoms in dementia with Lewy bodies may result from pathology in peripheral autonomic ganglia or central autonomic pathways.

have been relatively small and occipital hypometabolism has also been reported in PD without dementia.

Delusions are common in DLB, as in other dementias. In some patients they may relate to the visual hallucinations. Depression may also occur in DLB, particularly early in the course of dementia. Apathy, while again not specific for DLB, can be very prominent. As dementia progresses, symptoms such as anxiety and agitation often develop and may need treatment.

Sleep Disorders

REM sleep behavior disorder (RBD) occurs frequently in patients with α -synuclein pathology, including DLB, PD, and multiple system atrophy (Boeve et al, 1998; Boeve et al, 2004). It may precede these disorders by years, consistent with the concept of spread of α -synuclein pathology from the reticular activating system and nuclei such as the locus ceruleus to the substantia nigra and later to limbic and cortical regions. In RBD, lack of motor inhibition occurs during REM sleep. This leads to patients appearing to act out their dreams, and periods of REM sleep are accompanied by shouting, thrashing, punching, kicking, or other actions. These can be highly disturbing to the patient's bed partner. The history alone may be highly suggestive of RBD. A formal sleep study may be indicated if serious sleep disruption occurs in order to clearly document RBD. Other disturbances in sleep and arousal are common in DLB, including daytime drowsiness, obstructive sleep apnea (OSA), and periodic limb movements in sleep and may warrant investigation via polysomnography.

Autonomic Impairment

Autonomic impairment is well documented in DLB, as in other synucleinopathies such as PD and multiple system atrophy. The most serious symptoms

include orthostatic hypotension and syncope, but excess salivation, altered sweating, and seborrhea may also occur. Pathology in several pathways may predispose patients with DLB to syncope. Carotid sinus sensitivity has a higher frequency in DLB than in the elderly or in AD. Cardiac autonomic denervation may be shown by metaiodobenzylguanidine (MIBG) scintigraphic scanning. Autonomic symptoms may arise from α -synuclein pathology in central autonomic pathways or in the cell bodies of neurons in paraspinal autonomic ganglia.

DIAGNOSTIC EVALUATION OF DEMENTIA WITH LEWY BODIES

The current guidelines for the diagnosis of DLB consist of central, core, suggestive, and supporting features. The central feature of dementia allows patients with relatively minor impairment of memory but significant impairment of visuospatial or executive function to be included, as well as patients with more obvious memory impairment. It is unclear from published series on DLB whether there are patients who have intact memory but otherwise would meet criteria for dementia. The three core features are fluctuating level of alertness or cognition, spontaneous parkinsonism, and visual hallucinations. Two core features, or one core plus one suggestive feature, qualify as probable DLB. One core feature without a suggestive feature defines possible DLB. For example, progressive dementia with fluctuation and visual hallucinations, or with visual hallucinations and RBD could qualify as probable DLB. These revised criteria now need to have their sensitivity and specificity established in reference to neuropathology.

The basic clinical approach to dementia applies to DLB, namely, obtaining a history from an informant to document the onset, progression, and pattern of cognitive decline and the

resulting functional impairment, and confirming cognitive impairment by testing the patient's cognition. In many patients with DLB, the major differential diagnosis will be that of AD (**Case 3-1**). The age at onset of most patients with DLB ranges from 60 to 90, although younger patients, particularly those with a genetic predisposition to PD, have been documented. DLB is slightly more common among men than women, but this cannot be used as a diagnostic feature. Routinely inquiring about marked fluctuation, visual hallucinations, and symptoms of RBD will help to differentiate between DLB and AD. Difficulties can arise because elderly patients, in particular those with dementia, are prone to delirium due to an intercurrent illness or medi-

cation side effect; this is not evidence of fluctuation. Questionnaires have been developed to probe about cognitive fluctuation or alterations in wakefulness and vigilance, but their usefulness requires further study. The neurologic examination should allow parkinsonism to be identified and characterized. Problem areas are how much weight to assign to minimal parkinsonian features that can be associated with aging (eg, slowed gait, softer voice, and mild stooped posture) and to features that arise nonspecifically in moderate to severe dementia.

Severe neuroleptic sensitivity remains a suggestive feature in the revised criteria. This is of limited diagnostic value, particularly early in the disease course, because clinicians would not expose

Case 3-1

A 68-year-old man had the gradual onset of forgetfulness for approximately 1 year. Family members also noted that he sometimes appeared to briefly blank out during conversations. On assessment, his MMSE was 27/30, with impaired orientation and recall; on neuropsychological testing, there was impaired memory and executive function. Neurologic examination was notable only for a slightly stooped posture. The patient received a diagnosis of mild AD and was started on donepezil.

Eighteen months later, the patient had episodes of seeing people who were not there. These began while he was being treated for a urinary tract infection but persisted for months. He reported seeing children or sometimes animals in the room for minutes at a time and was not sure whether they were real or not. His wife reported that he was now sleeping poorly at night with very vivid dreams during which he would thrash or kick in bed and sometimes yell incoherently. The patient would often doze during the day. His MMSE was now 22/30, and he had marked difficulty drawing the numbers on a clock and drawing the hands to show the time. Motor examination revealed a soft voice and decreased blinking. No tremor was present. The patient needed to use his arms to arise from a chair and had a clear stoop. There was slight slowing and shuffling of gait. Twelve months later, the patient still reported visual hallucinations, eg, children walking in the garden past his window. He had decreased interest in activities and slept a lot during the day. His MMSE was 15/30. He had a softer voice, an obviously slowed gait, and difficulty turning.

Comment. This case illustrates convergence with AD early in the course. The visual hallucinations, symptoms suggestive of RBD, and parkinsonism early in the course of dementia point to DLB. Clinical progression on the MMSE is more rapid than that usually seen in AD.

KEY POINTS:

- Routine laboratory studies are of limited value in the diagnosis of dementia with Lewy bodies.
- Parkinson's disease with dementia may be clinically indistinguishable from dementia with Lewy bodies.

a patient with DLB to neuroleptics if atypical antipsychotics were available, and it is unethical to administer a test dose of a neuroleptic.

Laboratory investigations play a limited role in the routine evaluation of DLB at present, although some interesting findings have emerged from research studies. At present MRI or CT of the brain is used mainly to rule out structural CNS pathologies rather than to identify patterns consistent with DLB. History, examination, or imaging findings of stroke affecting the basal ganglia may point to vascular contributions to parkinsonism and dementia rather than DLB. Direct biomarkers of DLB, eg, imaging of α -synuclein lesions in the brain or measuring α -synuclein or related proteins in body fluids, do not yet exist. Indirect evidence of damage to nigrostriatal dopaminergic nerve terminals can be obtained by SPECT imaging, using radionuclide tracers such as β -citalopram, or PET images of fluorodopa uptake. Low striatal dopamine transporter activity occurs in DLB but not in AD and may be useful in differential diagnosis; it is now included as a suggestive feature (O'Brien et al, 2004). Other imaging methods also may have value but have received less study or show greater overlap with AD, and have been placed in the supporting feature category in the revised DLB criteria. Volumetric MRI measures show a degree of atrophy of the medial temporal lobe and hippocampal formation in DLB that is less than that found in AD (Barber et al, 2000). Occipital lobe hypometabolism has been found on PET or SPECT scans in DLB and PDD but not in AD (Minoshima et al, 2001). Evaluating peripheral sympathetic cardiac innervation by MIBG scintigraphy was recently proposed to be a marker related to synuclein pathology (Taki et al, 2004). At present, these are tools used more in research than in routine clinical practice, but they have been

acknowledged as suggestive features in the revised diagnostic criteria.

PARKINSON'S DISEASE WITH DEMENTIA AND THE DEMENTIA WITH LEWY BODIES SPECTRUM

Subtle cognitive impairment can be documented on sensitive psychometric testing in patients with even mild PD. For example, a community-based study of incident PD found that 36% of patients had cognitive impairment, which fell within the range of dementia in 8% (Foltnie et al, 2004). The risk of dementia increases in PD in association with age and duration and severity of parkinsonism. Formal criteria for PDD have not yet been developed. If conventional criteria for dementia are applied, a major challenge is to determine whether functional decline in PD is due to cognitive impairment or to motor effects of severe parkinsonism. PDD shows much commonality with DLB, including a high prevalence of visual hallucinations, and neuropathology of widespread α -synuclein lesions in limbic and often neocortical regions in addition to the brain stem (reviewed in Emre, 2003). Limited studies have compared cognitive, motor, and neuropsychiatric features in DLB and PDD. The differences appear to be largely quantitative, eg, greater neuropsychiatric symptom frequency or severity in DLB and more severe parkinsonism in PDD. Measures of fluctuating attention (Ballard et al, 2002) and overall cognitive profiles (Aarsland et al, 2004) show similar patterns of deficits in DLB and PDD.

MANAGEMENT OF DEMENTIA WITH LEWY BODIES**General Approaches**

Nonmedication aspects of management are important. Caregivers or family members need to be informed about the disease, its features and effects,

and about actions and interventions that they can undertake to promote safety, appropriate cognitive and social stimulation of the patient, and efforts to maintain muscle strength and mobility. Community resources and support groups such as the Lewy Body Disorders Association (<http://www.lewybodydementia.org>) can provide helpful information.

Patients with DLB tend to be very sensitive to medications and have a high risk of developing side effects of CNS-active drugs. Because of the diverse range of symptoms associated with DLB, it is often necessary to treat with a number of medications simultaneously. Some general guidelines may be helpful. Almost all symptomatic medications should be started at low doses and titrated carefully, with assessment of target symptoms as a positive outcome and monitoring for side effects or exacerbation of other features of the disease. “Start low and go slow” is sound advice. It is generally best to introduce one new medication at a time in order to make outcomes interpretable. However, it may be necessary to use combinations of medications targeting different domains or symptoms simultaneously and to fine-tune these. For example, use of a selective serotonin reuptake inhibitor (SSRI) for depression or apathy, together with a low dose of levodopa for parkinsonism, an acetylcholinesterase inhibitor for cognitive problems, and an atypical antipsychotic to control hallucinations may be necessary for optimal symptom control. Because of the possibility of drug-drug interactions, it is also advisable to stop medications after a reasonable trial if they are not having a clear benefit.

As yet, no drugs have been shown to have disease-modifying actions in DLB. This is a major unmet need. Disease-modifying approaches to PD

are receiving great interest, and it is possible that medications developed for PD may be applicable to DLB. Because the pathology of many patients with DLB includes deposition of amyloid β -protein, it is also possible that anti-amyloid treatments could have utility in DLB.

Table 3-2 groups a number of target symptoms by domains and lists some suggested medications. Few evidence-based recommendations for treatment in DLB are available, and the following discussion includes extrapolations wherever possible from clinical trials on patients with other dementias (mainly AD) or on symptom control in the elderly population and in some instances reflects the author’s personal experience and opinion.

Treatment of Specific Symptoms in Dementia With Lewy Bodies

Parkinsonism. A trial of levodopa is recommended. Because this medication may worsen neurobehavioral symptoms, a low dose should be started and increased slowly. The clinical response to levodopa is often less dramatic in DLB than in idiopathic PD (Molloy et al, 2005), and if no obvious improvement of parkinsonism occurs, the medication should be stopped. Dopamine agonists are not recommended because of higher risk of provoking behavioral symptoms or other side effects. Anticholinergic medications should be avoided because they may cause confusion or worsen cognitive performance.

Cognitive impairment and fluctuation. Biochemical studies have found a severe cholinergic deficit in limbic and cortical regions in DLB, raising the possibility that these patients may be particularly responsive to acetylcholinesterase inhibitors (AChEIs) such as donepezil, rivastigmine, or galantamine. Randomized clinical trials of AChEIs in DLB with 20 weeks of treatment

KEY POINT:

- The severe cholinergic deficit in limbic and cortical regions is the basis for using cholinesterase inhibitors in the treatment of dementia with Lewy bodies.

TABLE 3-2 Symptomatic Treatment in Dementia With Lewy Bodies

Target Symptoms	Drugs	Dosing	Comments
Cognitive Impairment			
Forgetfulness, poor attention, fluctuation	AChEIs: donepezil	5 mg/d × 4 weeks, then 10 mg/d	Gastrointestinal side effects may limit dosing of AChEIs.
	Rivastigmine	1.5 mg bid, increase in 1.5-mg steps q 2 to 4 weeks, maximum 6 mg bid	AChEIs only rarely worsen parkinsonism.
	Galantamine	8 mg/d orally, increase to 16 mg/d, maximum 8 mg/d (See Table 2-8)	Urinary frequency and increased saliva and tearing may occur.
Apathy, decreased initiative	Selective serotonin reuptake inhibitor, serotonin-norepinephrine reuptake inhibitor	Depends on specific drug	Tricyclics should be avoided (decreased cognition, orthostasis).
Psychomotor slowing	AChEIs	See above	
	Methylphenidate	2 mg to 5 mg qd, can increase by 2.5 mg to 5 mg every 5 days, dose bid, AM, and noon, maximum 20 mg/d	Discontinue if no benefit.
	Amphetamine	5 mg qd, increase by 5-mg steps, q 7 days, dose AM and noon, maximum 25 mg bid	Discontinue if no benefit.
Neuropsychiatric Symptoms			
Hallucinations, delusions	AChEIs	See above	
	Clozapine	12.5 mg qhs, increase in 12.5-mg steps, maximum 50 mg tid	Agranulocytosis.
	Risperidone	0.5 mg qhs, increase in 0.5-mg steps, q 7 days, divided bid, maximum 1.5 mg bid	Parkinsonism may worsen.
	Olanzapine	2.5 mg qhs, increase in 2.5-mg to 5-mg steps, q 7 days, maximum 10 mg bid	Parkinsonism may worsen.

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TABLE 3-2 *Continued*

Target Symptoms	Drugs	Dosing	Comments
Agitation, insomnia	Aripiprazole	5 mg qd, increase in 5-mg steps, q 2 weeks, maximum 15 mg/d	Untested in dementia with Lewy bodies but well tolerated in Alzheimer's disease
	AChEIs	See above	
	Atypical antipsychotics	See above	
	Trazodone	50 mg qhs, increase in 25-mg to 50-mg steps to maximum 200 mg qhs	
Depression	Chloral hydrate	500 mg qhs, can increase in 500-mg steps to maximum 1500 mg qhs	Best as on-needed basis, not chronic dosing
	Fluoxetine	10 mg qd × 4 weeks, increase in steps, maximum 40 mg qd	
	Paroxetine	10 mg qd, increase by 10 mg q 2 to 4 weeks, maximum 40 mg/d	
	Sertraline	25 mg qd, increase in 25-mg steps, q 2 to 4 weeks, maximum 200 mg qd	
Anxiety	Citalopram	10 mg qd, increase in 10-mg steps, q 2 to 4 weeks, maximum 60 mg/d	Escitalopram is similar.
	Paroxetine	See above	
	Sertraline	See above	
Motor Impairment	Buspirone	5 mg bid, increase by 5-mg steps, maximum 60 mg/d	
	Levodopa/carbidopa	10 mg/100 mg start bid or tid, titrate very slowly, can use 1/2 tablets	Hallucinations, anxiety, agitation, sleepiness
	Dopa agonists	Best avoided	Higher risk of hallucinations in dementia with Lewy bodies
Sleep Disorders			
REM sleep behavior disorder	Clonazepam	0.25 mg qhs, increase in 0.25-mg steps q week, maximum 1 mg qhs	Sedation

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TABLE 3-2 *Continued*

Target Symptoms	Drugs	Dosing	Comments	
Daytime somnolence	Melatonin	3 mg qhs, increase in 3-mg steps to 12 mg qhs	Unclear if long-term benefits are maintained	
	Methylphenidate	See above		
	Amphetamine	See above		
Autonomic Impairment	Modafinil	100 mg q AM, increase in 100-mg steps q week, max 400 mg q AM	Approved for narcolepsy, limited evidence for use in daytime somnolence	
	Orthostasis	Fludrocortisone	0.1 mg qd to 0.3 mg qd	Fluid retention, edema
		Midodrine	5 mg tid to 10 mg tid	

AChEI = acetylcholinesterase inhibitor; q = every; bid = 2 times a day; qd = every day; qhs = at bedtime; tid = 3 times a day.

(McKeith et al, 2000) and PDD with 24 weeks of treatment (Emre et al, 2004) have been conducted. With 60 subjects in each arm, the DLB trial was underpowered and showed no significant effect on the MMSE, marginal findings on behavioral measures, and significant improvement on computerized tests of attention. The PDD trial showed favorable treatment-placebo differences in measures of cognitive function (including computerized timed tests of attention), global ratings, and activities of daily living. Although enhancing cholinergic activity could worsen parkinsonism, this was only rarely seen in the clinical trial of rivastigmine for DLB. In patients with PDD, rivastigmine usually did not worsen parkinsonism, although 10% of patients showed worsening of tremor (Emre et al, 2004). Gastrointestinal side effects were the most common reason for discontinuation of study drug. Further clinical trials of AChEIs in DLB and PDD are needed. However, it seems reasonable to undertake a trial of one of these medications to see whether

it improves or stabilizes cognitive abilities or fluctuation.

Apathy and decreased initiative can contribute to cognitive impairment but are difficult to treat. Although levodopa may help to a degree, other medications may be worth considering. Possibilities include trials of SSRI or serotonin-norepinephrine reuptake inhibitor antidepressants or stronger stimulants such as methylphenidate or even amphetamine. If there is no benefit, these drugs should be stopped.

Hallucinations, psychosis, and agitation. Visual hallucinations may only need drug treatment if they are disturbing to the patient. If treatment is needed, AChEIs sometimes help (McKeith et al, 2000). Typical neuroleptics should be avoided because of risks of worsening parkinsonism or causing severe reactions with cognitive and motor decline (neuroleptic sensitivity), and medications such as olanzapine and risperidone should be used cautiously because they have weak D2 receptor-blocking activity. Atypical

antipsychotic agents, such as quetiapine or clozapine, may be considered. Clinical trials support their use in PD with psychotic symptoms (reviewed in Miyasaki et al, 2006) although they have not yet been formally studied in DLB. Aripiprazole is effective in treating psychotic symptoms in AD and could also be considered in DLB and PDD.

For agitation, many treatment options are possible. Environmental and interpersonal triggers of agitation should be sought when taking the history. If levodopa doses are relatively high, reduction may lead to decreased agitation. Many classes of medications are available, and the guiding principle of treatment is to try to achieve control without overly sedating patients. Most of these are drawn from studies of dementia, most commonly AD (Schneider et al, 2006). Antipsychotic agents, chloral hydrate, trazodone, and anti-convulsants such as valproate may be considered.

REM sleep behavior disorder and sleep disorders. Features of OSA may overlap with those of RBD; therefore, treatment of sleep disruption may be guided by findings on polysomnography. Nasal continuous positive airway pressure may improve symptoms if OSA is present. To control RBD, clonazepam is the first-line choice, starting at 0.25 mg at night, and it can be titrated up to a maximum of 1 mg. It is generally well tolerated and rarely causes worsening of cognition or of daytime somnolence. Melatonin may also be used, alone or together with clonazepam (Boeve et al, 2004). Patients with difficult-to-control sleep problems may benefit from assessment by a specialty sleep disorders clinic.

For insomnia, similar medications to those used for agitation may be considered, as well as low doses of benzodiazepines such as zolpidem. Newer sleep-promoting agents, such

as eszopiclone, zaleplon, and extended release zolpidem, have not yet been formally studied in patients with DLB but appear to have favorable profiles of promoting sleep without inducing tolerance or causing excessive daytime sedation. **Case 3-2** illustrates symptomatic treatment for a patient with DLB.

FUTURE DIRECTIONS

Now that the recent changes to the DLB clinical diagnostic criteria have been proposed, their accuracy will need to be examined. Comparisons with PDD will form an important component. The broader clinical picture of Lewy body disorders may facilitate studies into earlier diagnosis. Clinical methods may include sensitive neuropsychological methods to identify profiles of cognitive impairment at an early stage of PD or DLB, in particular aimed at visuoperceptual function or fluctuation. Patients with precursors to DLB and PDD such as RBD will be studied in greater depth and followed. Biomarkers, including tests based on blood and CSF, and imaging modalities will continue to be pursued. The most critical need is a marker related to α -synuclein pathology. As is the case for biomarkers in general, their usefulness needs to be established in relation to the clinical evaluation, eg, whether they help to identify patients with minimal clinical symptoms or even preclinically.

The prevalence of DLB and PDD and risk factors will be studied. This will include the important area of genetics. Recent findings in the genetics of PD will be applied to PDD and DLB. A promising lead has been the finding of duplication (Chartier-Harlin et al, 2004) or triplication (Singleton et al, 2003) of the α -synuclein gene in rare families with autosomal dominant PD, and some members of these families have shown dementia and diffuse Lewy body

KEY POINTS:

- Visual hallucinations may only need drug treatment if they are disturbing to the patient.
- Atypical antipsychotics are strongly preferred for treatment of psychosis in dementia with Lewy bodies.

Case 3-2

A 74-year-old man had the gradual onset of forgetfulness and decreased initiative and interest in activities for 12 months, accompanied by sleeping “a lot” during the day. His wife noted episodes of kicking and sometimes moaning during his sleep for about 4 years. In the past few months, slowing of his gait occurred. Mental status testing was notable for an MMSE score of 23/30. A brain MRI showed mild cortical atrophy with no evidence of focal lesions. A sleep study documented RBD. The patient was started on donepezil and titrated to 10 mg/d. Subsequently, clonazepam 0.5 mg was added at night. The patient’s MMSE was 25/30 on follow-up 4 months later, but his wife complained that he still had decreased interest in activities. His mood was a little flat but not clearly depressed. His gait was a little slower, and he had had two falls, associated with tripping at curbs. Carbidopa/levodopa 25 mg/100 mg was started 2 times a day and increased to 3 times a day after 1 week. The patient’s gait improved a little, but he became anxious. Over the next few months he became more withdrawn and apathetic. Sertraline was started at 25 mg/d, and increased to 50 mg/d with slight improvement in his level of interest and decreased anxiety. A few months later, his MMSE dropped to 20/30. The patient reported visual hallucinations. He claimed to see people in the house, particularly at night. Although they did not talk to him, he thought that they were threatening him. The patient became restless. His gait was slowed, with decreased arm swing, but there was no postural instability. The carbidopa/levodopa was decreased to 2 times a day, but the hallucinations persisted and his walking worsened. The dose of carbidopa/levodopa was restored to 3 times a day. Quetiapine 25 mg was added during the day and at night for the hallucinations, with almost complete resolution. A few months later, the patient had two falls and complained of dizziness when standing up. Examination revealed a drop in blood pressure from 130/80 mm Hg to 112/60 mm Hg that accompanied the complaint of dizziness. Further slowing of gait and postural instability occurred. The patient’s MMSE score was 17/30. Elastic stockings were tried, but the patient found them too uncomfortable to wear. Fludrocortisone was added at 0.1 mg/d, which led to improvement. In addition, he was prescribed a quad cane to assist his walking, and he had no further falls over the next 4 months.

The patient was brought to clinic urgently 1 month later with increased apathy and confusion and decreased appetite. General examination was notable for a low-grade fever. On the MMSE he scored 10/30, and he had marked cognitive slowing. He had great difficulty rising from a chair and initiating gait. Laboratory tests were notable for an increased white blood cell count and greater than 100,000 bacteria in his urine. Following treatment with antibiotics, his condition improved; 1 month later his MMSE was 17/30, and he was able to walk as before, using a cane.

Comment. This case illustrates the complex range of symptoms and treatment issues that arise in managing a patient with DLB. It is important to consider reversible factors such as acute infections, dehydration, or medication side effects if patients show increasingly rapid deterioration.

pathology at autopsy. Polymorphisms in promoter regions of the α -synuclein gene have shown association with DLB in some but not all studies.

Treatment of the symptoms of DLB will require more rigorous study, but being able to pool DLB and PDD patients for certain types of interventions may facilitate the conduct of clinical trials. A major unmet need is finding disease-modifying approaches for DLB. Animal and cellular models have exploited α -synuclein to recapitu-

late aspects of Lewy body pathology, but the pathogenesis of α -synuclein aggregation and its toxicity to neurons and glia are incompletely understood. Lead compounds are being tested, and some have emerged for clinical trials in PD. Designing disease-modifying clinical trials in DLB and PDD will be a challenge and may require information for all of the areas mentioned above, combining knowledge of risk factors and early diagnosis with sensitive clinical and biomarker outcome measures.

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