LEWY BODY DEMENTIA

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Dementia is becoming increasingly prevalent since elderly patients are living longer due to the development of treatments for other diseases and conditions. The percent of our population over 60 is also increasing with the wave of aging baby boomers. Additionally, more individuals seek medical assistance for cognitive problems as visibility for treatments improves. This combination of factors results in the dementia syndromes becoming more common, causing physicians to encounter more patients with dementia as well as more caregivers of these patients.

Of dementia subtypes, Alzheimer's disease (AD) is the most common. Dementia with Lewy bodies (DLB) is thought to be the second most common subtype. DLB's typical symptoms include cognitive impairment, visual hallucinations, spontaneous parkinsonism, and fluctuating confusion. Supportive features include a variety of sleep disruptions that may occur before manifestations of dementia. Psychiatric symptoms include vivid visual hallucinations and depression. The clinical features of DLB are strikingly similar to those of dementia in Parkinson's disease (PD).

The underlying biology of DLB is complex, but the presence of alpha-synuclein containing Lewy bodies (LB) is a common factor. These inclusions also contain ubiquitin. PD dementia shares these pathological findings with DLB, as well as neural degeneration of the substantia nigra. DLB and dementia in PD may represent the same pathological process along a disease spectrum.

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Additionally, many DLB cases are also associated with beta-amyloid and tau-containing neurofibrillary tangles, features that are associated with AD. Frequently, AD patients are also found to have LB. The reason for this overlap is unknown. However, the greater the Alzheimer's pathology in DLB patients, the more the clinical features of DLB overlaps with AD.

In this chapter, we will review DLB including clinical, pathological, and radiological features as well as biomarkers and treatments.

I. Introduction

Dementia is defined as a syndrome of progressive cognitive impairment that interferes with daily function (DSM IV-TR, 2004). The cognitive areas involved include memory, language, abstract thinking, visuo-spatial skills, behavior, and personality. Alzheimer's disease (AD) is the most common dementia subtype, representing over half of all dementias. Dementia with Lewy bodies (DLB) is the second most common type of dementia at 20%, affecting 15–25% of elderly demented patients (McKeith *et al.*, 1996). Of those patients with Parkinson's disease (PD), 30% will develop dementia during the course of their illness (Emre *et al.*, 2007). Many more Parkinson's patients will experience some type of cognitive change. Table I compares the most common forms of dementia.

The four main components of the DLB syndrome are dementia, visual hallucinations, parkinsonism, and fluctuation of symptoms, particularly confusion. The cognitive decline associated with DLB includes pronounced variation in attention and alertness. Visual hallucinations are recurrent, consist of formed or detached figures and typically occur early in the disease course. The parkinsonian motor features include myoclonus, bradykinesia, rigidity, and less commonly tremors. Additional associated features include sleep anomalies, repeated falls, syncope, transient loss of consciousness, delusions that are often paranoid, urinary incontinence, and depression. DLB patients are sometimes oversensitive to neuroleptic agents, and use of such medication may precipitate a change in functional status.

DLB exhibits a clinical overlap with both the dementia of AD and the motor symptoms of PD. DLB is characterized by intracytoplamic proteinaceous inclusions called Lewy bodies (LB). These collections of alpha-synuclein (AS) plaques occur throughout the cortex and subcortical regions. Additionally, DLB has a loss of acetylcholine producing neurons similar to those seen in AD and a loss of dopaminergic neurons, as seen in PD.

This chapter will review DLB clinical and pathologic features, radiographic findings, biomarkers, and current treatment modalities.

TABLE I
COMPARISON OF THE MOST COMMON FORMS OF DEMENTIA

	Epidemiology	Pathology	Clinical features
Alzheimer's disease	Most common >65 years old	General cortical atrophy, especially in medial temporal lobe	Memory impairment
	Genetic susceptibility factors (mostly for late-onset)	Amyloid plaques in cortex	Difficulty in learning new information
	Autosomal dominant inheritance (more often present in early onset)	Neuritic plaques	Little fluctuation or hallucinations
		Neurofibrillary tangles containing tau and ubiquitin	Apraxia
		Amyloid angiopathy	Rigidity may be a late feature
Vascular dementia	>40 years old	Multiple infarcts—often in subcortical areas	Step-wise deterioration
	Risk factors:		May improve
	Hypertension	Fibrous and hyaline degeneration of small arteries	Pyramidal signs
	Smoking		
	Vascular disease		
	Other vascular risk factors	White matter infarction	Pseudobulbar palsy
Dementia with Lewy body (DLB)	Usually sporadic	General cortical atrophy; may be normal	Parkinsonism
	Often elderly, especially when cognitive presentations	Depigmentation of substantia nigra	Fluctuating mental state with slow processing, attentional, and visuo-spatial problems
		LB in limbic and cortical neurons; often brainstem LB	Visual hallucinations
		Amyloid deposits are common	Neuroleptic sensitivity
			REM behavioral disorder
Parkinson's disease dementia	30% of PD patients	Neuronal cell death in substantia nigra	Parkinsonism before onset of dementia
	Usually sporadic	LB in nigral neurons; often in limbic and cortical regions	Fluctuating confusion with similar features (attentional problems, slow processing) to DLB
			Visual hallucinations

II. DLB Clinical Features

In 2005, the DLB consortium issued its third report on the Current International Consensus Diagnostic Criteria for DLB (McKeith *et al.*, 2005). The central features necessary for a diagnosis of DLB include the presence of a dementia, fluctuating cognition, hallucinations, and parkinsonian symptoms. Numerous supportive features are commonly found in DLB patients, but are not necessary for the diagnosis.

As in AD, DLB patients have a progressive cognitive decline sufficient enough to interfere with normal social or occupational functioning (DSM IV-TR, 2004). However, in contrast to AD, the memory impairment of DLB may not be prominent in the early stages (McKeith *et al.*, 2005). The cognitive problems fluctuate with pronounced variation in attention and alertness. This feature is hard to monitor in clinical practice due to its difficulty to observe on a consistent basis. When they do appear, the deficits on tests of attention, executive function, and visuo-spatial ability in DLB are generally prominent (McKeith *et al.*, 2005). Subjects with DLB have better delayed memory and spared recall, but worse executive function and visuo-spatial abilities than patients with early AD. Such differences in visuo-spatial abilities can be demonstrated by the intersecting pentagons used as part of the mini mental-status exam. An example of this is shown in Fig. 1.

In DLB, the cognitive deficits represent both cortical and subcortical impairments, with greatest deficits being verbal fluency, visual perception, and performance tasks while there is preservation of confrontation naming, recognition, and short-term recall (Connor *et al.*, 1998; Mormont *et al.*, 2003; Walker *et al.*, 1997).

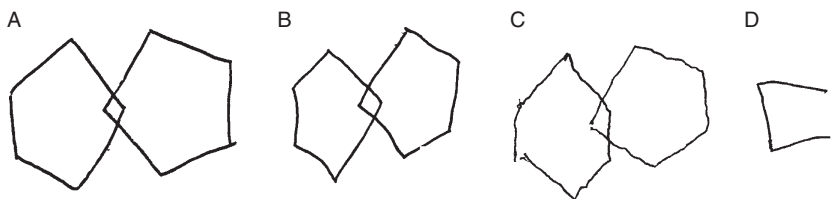

FIG. 1. Figure drawings of normal, Alzheimer's dementia, and Dementia with Lewy body (DLB) patients. Patient drawings demonstrate the visuo-spatial dysfunction in DLB patients compared with normal aging patients and AD patients. Image A is a model of connecting pentagons, normally used to test visuo-spatial function. The patient is asked to copy this image during the test. Image B shows a normal patient's response. Note that this image has five sides and that the adjacent sides intersect in both pentagons. Image C is drawn by an AD patient. This subject drew a hexagon rather than a pentagon. This is a cognitive error. Image D is from a patient meeting the criteria for probable DLB. There is marked loss of visuo-spatial relationships, and it is hard to tell what they are trying to copy.

Both DLB and Parkinson's disease dementia (PD-D) patients have more pronounced subcortical cognitive impairment profiles with less marked memory impairment than AD patients. However, those patients with a pattern of prominent cortical involvement have more severe memory impairment like that of AD (Janvin *et al.*, 2006).

Recurrent visual hallucinations are prominent and are typically well formed and detailed in DLB patients. Hallucinations of animals and people are common. They are usually frightening and it is difficult to convince the patient that they are not real. This may pose safety problems, as the patient will feel that they will be attacked or their home invaded. In contrast, visual hallucinations are uncommon in AD, particularly early in the disease course. Therefore, report of such vivid hallucinations in the context of dementia should alert the physician to the likelihood of DLB. LB concentrations in the posterior temporal lobes and amygdale, areas critical for emotion and visual processing, are associated with the presence of these hallucinations (Harding *et al.*, 2002). As such, it has been speculated that visual hallucinations are positive phenomenon, caused by an irritating effect of the LB in relevant areas.

The onset of parkinsonian symptoms occurs spontaneously in DLB. At the time of diagnosis, approximately 50% of DLB patients have extrapyramidal motor symptoms, with 75% developing them during some stage of the disease course (McKeith *et al.*, 1992b). Patients have postural instability, gait disorders that may be characterized by hunched posture and festination, and facial immobility (Burn *et al.*, 2003). Tremor may be present, but is not as prominent as in PD. The Unified PD Rating Scale can be used to monitor parkinsonian progression, but only for those symptoms that can be assessed in the face of dementia (Fahn *et al.*, 1987). Objective findings include tremor at rest, intention tremor, bradykinesia, rigidity, and facial expression. When compared to AD patients of a similar cognitive level, DLB patients have greater functional impairment due to the presence of extrapyramidal symptoms (McKeith *et al.*, 2005).

Many DLB patients have parasomnias. The most common is REM behavioral disorder (RBD) which often begins concurrently or after the onset of parkinsonism or dementia (Boeve *et al.*, 2007). It is marked by lack of muscle atonia in the presence of vivid dreams. In RBD that lack of muscle paralysis allows the patient to engage fully in the physical activities of the dream, resulting in vocalizations and sometimes wildly violent behavior. Patients are often unaware of the disorder, but bed partners may report it as a presenting symptom when asked. RBD is associated with daytime somnolence. It can be diagnosed by polysomnography which shows elevation in EMG tone during REM sleep and unusual movements during sleep (Fantini *et al.*, 2005).

DLB patients are notorious for their neuroleptic sensitivity, and reactions occur in 30–50% of DLB patients (Aarsland *et al.*, 2005b). Such neuroleptic

sensitivity reactions area characterized by sudden onset of impaired consciousness, acute confusion, psychotic episodes, and exacerbation of parkinsonian symptoms such as rigidity and immobility (McKeith *et al.*, 1992a). These reactions may even result in decreased survival within several days. A 2005 study by (Aarsland *et al.*, 2005b) demonstrated that there was a 58% frequency of neuroleptic sensitivity to olanzapine, with only 11% to clozapine and 6% to thioridazine. This confirmed previous studies that showed unacceptable safety profiles for some neuroleptics in LB dementias. Additionally, DLB patients are often activated by sedatives and awakened by sleep medications (Rogan and Lippa, 2002).

Other common findings in DLB include autonomic instability which results in orthostatic hypotension and urinary incontinence. Falls may be frequent, and can be the result of truncal ataxia or syncope. Hallucinations of other modalities, depression, and severe delusional symptoms may be present. Transient episodes of loss of consciousness occur and are often unexplained. Increased fluctuations of consciousness have been associated with increased thalamic and decreased occipital perfusion (O'Brien *et al.*, 2005).

III. PD-D

PD-D is a dementia syndrome that develops in the context of an established PD. PD-D has an insidious onset with slow progression, and is defined as having impairment in more than one cognitive domain representing a decline from premorbid level. The deficits present must be severe enough to impair daily life and the deficits must be independent of the impairment by motor or autonomic symptoms (Emre *et al.*, 2007). Such impairments may affect social functioning, occupational productivity, or personal care.

PD-D patients share many common deficits with DLB patients. PD-D patients demonstrate fluctuating impaired attention with difficulty in preforming tasks. Executive functions are impaired especially with tasks that require initiation, planning, and concept formation. Bradyphrenia is common. Visuo-spatial functions are impaired with problems of orientation, perception, and construction. Memory impairment is greatest in recalling recent events and new information, but memory can improve with cueing. Core language functions are preserved, but word recall and complex sentence comprehension may be limited. PD-D patients are often apathetic, with concomitant anxiety and depressive symptoms. Visual hallucinations are complex and include formed visions of people, animals, or objects. Delusions are often paranoid, and patients suffer from sleep disorders that result in daytime somnolence.

IV. DLB and PD-D

There is no clinical rational or pathological basis that determines a definite time interval between development of motor symptoms and onset of dementia in differentiating PD-D from DLB. In general, a diagnosis of PD-D should be made when dementia develops within the context of established PD, while DLB should be diagnosed when dementia occurs before or concurrently within 1 year of parkinsonism (McKeith *et al.*, 2005).

Often patients do not fit into either pattern above. Many times early cognitive change is recognized in patients with PD, or DLB patients present with parkinsonism at the same time as their cognitive symptoms. The neuropsychological profiles in DLB and PD-D share basic similarities with abnormalities in attention, executive function, visuo-spatial function, language function, memory retrieval, and behavior (Lippa *et al.*, 2007a,b). There is no symptom or sign that absolutely distinguishes DLB and PD-D, as both have fluctuating cognitive dysfunction, visual hallucinations, parasomnias, and autonomic dysfunction.

There are, however, some subtle differences that can be used to elicit a more precise diagnosis. DLB patients make executive function errors (Aarsland *et al.*, 2003), and have more hallucinations and psychosis than PD-D patients (Mosimann, 2006). DLB patients have fewer parkinsonian signs than PD-D patients and little resting tremor. The parkinsonism of DLB is more weighted with generalized slowing with postural and gait disturbances (Burn and McKeith, 2003). They also have greater symmetry of their motor features than PD-D patients. Additionally, adverse reactions to antipsychotic agents may be greater in DLB patients.

V. Pathology

Found in 50% of dementia patients (Hamilton, 2000; Lippa *et al.*, 1998), the main identifying pathologic feature of DLB is the LB. LB are spherical intracytoplasmic protein deposits around the nucleus and throughout the dendrite of subcortical and cortical neurons. They consist of filamentous protein granules composed of AS and ubiquitin, and are surrounded by a halo of neurofilaments. Widespread LB differentiate the LB dementias from other dementia subtypes. The number of LB present does not correlate strongly with either the duration or severity of the dementia (Harding *et al.*, 2001). However, the number of cortical LB is variably correlated with the severity of DLB (Samuel, 1996). When located in the temporal lobe, LB are associated with the visual hallucinations of DLB (Harding *et al.*, 2002).

AS is a synuclein protein primarily found in the neocortex, hippocampus, substantia nigra, thalamus, cerebellum, and with the highest proportion in the basal ganglia (Rockenstein *et al.*, 2001). Cortical-LB sites include the cingulate gyrus, entorhinal cortex, insular cortex, frontal cortex, and amygdale. AS is a small protein that shares a structural resemblance with apolipoproteins (Mukaetova-Ladinska *et al.*, 2006). It is a neuronal presynaptic protein found widely in the central nervous system (CNS). Normally a soluble and unstructured protein, it can aggregate to form the insoluble neurotoxic fibrils that characterize LB. Epitope mapping shows similar patterns in AD, DLB, and PD (Lippa *et al.*, 2001).

A 2007 study by Kramer found that small individual AS aggregates are more common than LB. These aggregates are located at presynaptic terminals, and result in almost a complete loss of dendritic spines at the postsynaptic areas (Kramer and Schulz-Schaeffer, 2007). Additionally, AS has been found to have a role in the reducing dopamine synthesis (Mukaetova-Ladinska *et al.*, 2006). Although the mechanism of AS activity is incompletely understood, it is clear that it plays a large and complex role in the pathogenesis of DLB.

There is no clear pathologic differentiation between DLB and PD-D. Both disease entities result in end-stage disease with diffuse brain involvement and clinical phenotypes that are nearly indistinguishable. However, there are subtle pathological differences that can be seen at autopsy. Neuronal loss in the substantia nigra is greater in PD-D than in DLB, while beta-amyloid patterns are more consistent in DLB. AS pathology is greater in the striatum in DLB than PD-D (Duda *et al.*, 2002). The AS aggregates into fibrils in LB and Lewy neurites in DLB, PD-D, and PD, with the LB being indistinguishable between the syndromes. AS is the primary protein in all the LB, and solubility and epitope studies show similar features of the AS among the syndromes (Baba *et al.*, 1998). This suggests that DLB, PD-D, and PD may represent different points on a continuum of LB disorders, with motor and nonmotor features reflecting the regional burden and distribution of pathology.

Most patients with DLB also have pathology typically seen in AD patients. LB and Lewy neurites occur in cortical and brainstem nuclei in association with cortical-amyloid plaques and neurofibrillary tangles (McKeith *et al.*, 2004). The degree of AD characteristics seen in DLB patients correlates with the amount of AD pathology, with the main components seen being beta-amyloid and tau. Tau aggregates are known to increase the formation of LB in susceptible brain regions, such as the amygdale (McKeith *et al.*, 2004). This finding has been noted in both DLB and AD patients, showing significant overlap between the two types of dementia with regard to pathological findings (Figs. 2 and 3).

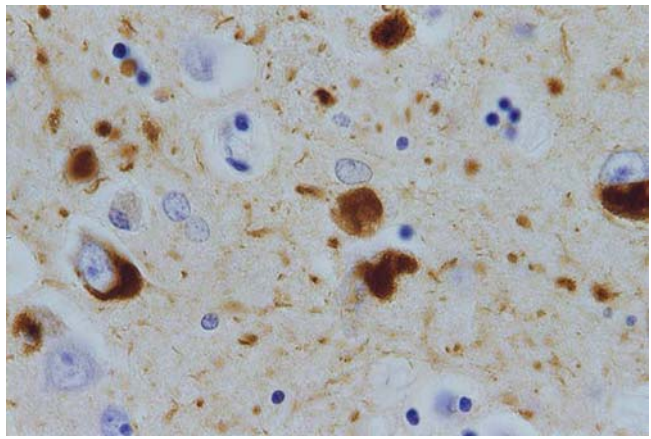

FIG. 2. Lewy bodies (LB) and Lewy neurites. This is a moderately high-power magnification of brain tissue from the amygdale of a patient with DLB. Tissue is stained with antibodies against alpha-synuclein (AS). It demonstrates numerous AS containing Lewy bodies and Lewy neurites.

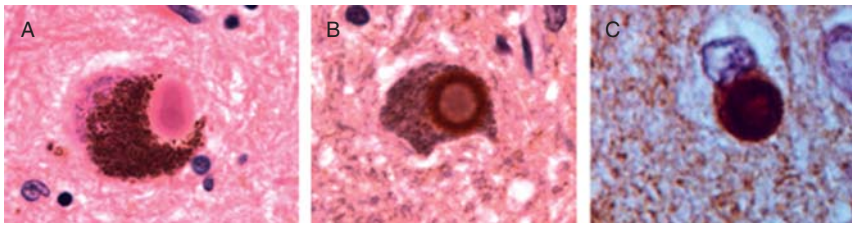

FIG. 3. High-power magnification images of LB. Image A is stained using a routine H & E stain. It shows the classical nigral LB with an eosinophilic core and clearer peripheral region. Note the neuromelanin pigment. Image B is a nigral LB from the same case, but stained with antibodies to AS. It demonstrates that AS is concentrated at the periphery of the LB (the clearer region on H & E stains). Image C shows a cortical LB stained with AS. These typically occur in smaller neurons, and they stain more uniformly with AS; cortical LB lack a halo.

VI. Genetics

In most cases, the LB diseases occur sporadically. Fully penetrate genetic causes for DLB are rare; however, there are likely additional genetic and environmental susceptibility factors that are still unidentified. There are a variety of genetic etiologies for dementia, with most being caused by abnormal CNS protein processing, expression, or aggregation. Many different types of cellular damage

cause aggregation of a variety of CNS proteins, and no single cause has been linked to dementias. Additionally, mutations causing dementia and Parkinsonism may lead to mixed or variable protein aggregates (Rajput *et al.*, 2006).

Genetic abnormalities in AS or other proteins that cause LB diseases are rare, but may lead to the cognitive or motor features of the disease. Dementia and parkinsonism are not always related to pathology; other genetic localizations may also lead to symptoms of parkinsonism and dementia. For example, some patients with tau mutations may have features of PD-D and DLB but lack LB, while others may have clinical and neuropsychological features that differ.

Factors determining the distribution of pathology in relation to the symptoms are incompletely understood. Schiesling *et al.* (2008) aptly stated that, "The identification of the first gene in familial Parkinson's disease (PD) only 10 years ago was a major step in the understanding of the molecular mechanisms in neurodegeneration. AS aggregation was not only recognized as a key event in neurodegeneration in patients carrying mutations in this gene, but it turned out to be the most consistent marker to define LB pathology also in nonheritable idiopathic PD." Numerous other genes have been found associated with PD, and many individuals with "idiopathic" forms may prove to carry susceptibility factors.

VII. Biomarkers

There are currently no highly sensitive clinical diagnostic criteria that distinguish DLB from other dementia subtypes with certainty, but this could be aided by biomarkers for DLB. Aarsland recently reviewed antemortem markers that aid in the diagnosis (Aarsland *et al.*, 2008). This study determined that, "The best evidence was for scintigraphy of the striatal dopamine transporter system using FP-CIT SPECT. Several small scintigraphy studies of cardiovascular autonomic function using metaiodobenzylguanidine SPECT have reported promising results. Studies exploring innovative techniques based on CSF have reported interesting findings for the combination of amyloid beta (abeta) isoforms as well as AS, and there are interesting results emerging from preliminary studies applying proteomic techniques." Other recent studies of modalities, including MRI scanning, SPECT, and EEG, were less useful for establishing a diagnosis in individual patients (Aarsland *et al.*, 2008). Of note, is the finding that DLB patients may show less medial temporal lobe atrophy on MRI when compared with the patients of AD (Lippa *et al.*, 1999). A large portion of future DLB research will be in field of identifying usable biomarkers to aid in clinical diagnosis.

VIII. Management

The treatment and management of DLB patients is complicated by their neuropsychiatric profile and extrapyramidal signs. Cognitive impairment must be addressed in the context of hallucinations, apathy, depression, and sleep disorders. Functional status is compounded by the increased morbidity of physical symptoms. Postural instability, continence, bradykinesia, syncope, falls, and autonomic instability worsen DLB functional impairment. All these factors must be considered when deriving a treatment program for the affected patient.

The management of DLB patients should focus on having an accurate diagnosis and identification of target symptoms that concern the patient and caregiver (Barber *et al.*, 2001). Nonpharmacological interventions such as physical and occupational therapy, community resources, and home care should be considered in addition to pharmacological interventions. Caregiver education is paramount because sometimes identifiable triggers for the patient's fluctuations can be identified.

Although there are no pharmacologic treatments aimed specifically at DLB, patient symptoms can be addressed by giving them the treatments for AD and PD. Medications should be kept to a minimum since adverse responses are not uncommon. In particular, traditional neuroleptics should be avoided, due to the high rate of severe neuroleptic sensitivity in DLB. Low-dose newer antipsychotic drugs are safer but sensitivity reactions have been documented and they should be monitored carefully (McKeith *et al.*, 2004).

DLB patients have greater cholinergic loss than AD patients (Perry *et al.*, 1994), and respond to cholinesterase inhibitors more effectively than AD patients (Samuel *et al.*, 2000). Significant improvement in fluctuating cognitive impairments, visual hallucinations, apathy, anxiety, and sleep disturbance are seen with cholinesterase inhibitors when used in the typical dose range for AD (McKeith *et al.*, 2004). Improvement of attention upon treatment was most notable in patients with visual hallucinations (McKeith *et al.*, 2004). Significant and extensive reduction in beta-amyloid deposits has been noted in DLB patients treated with cholinergic enhancers (Ballard *et al.*, 2007). Symptomatic response to cholinesterase inhibitors is comparable in PD-D and DLB, with neither having significant compromise of motor function (Burn and McKeith, 2003). Care should be used to monitor DLB patients for orthostatic hypotension when on cholinesterase inhibitors.

Dopaminergic therapy is the mainstay treatment for extrapyramidal symptoms in DLB and PD-D. The lowest effective level of levodopa should be used (McKeith *et al.*, 2004). Although the effectiveness in the LB dementias has not been extensively studied, the improvement of symptoms may be less than those seen in pure PD due to their additional intrinsic striatal pathology and dysfunction (Duda *et al.*, 2002).

Management of additional DLB symptoms is complicated. Depression is common in both DLB and PD-D and can be treated with selective serotonin reuptake inhibitors (McKeith *et al.*, 2005). RBD can be treated with clonazapam, melatonin, or quetiapine (Boeve *et al.*, 2004). Tricyclic antidepressants, low potency neuroleptics, antiparkinsonian anticholinergic drugs, and antispasmodics for bladder or gastrointestinal tract should be avoided in DLB and PD-D patients as they may not only worsen cognition and psychotic symptoms but may be associated with orthostatic hypotension (McKeith and Mosimann, 2004).

When treating dementia patients, physicians need to assess the individual needs of their patient. The safety and tolerability of pharmacologic agents should be considered, along with their risk of side effects and worsening of both motor and cognitive functioning in PD-D and DLB. It is also important to remember when treating these patients, that they are often frail and can clinically decompensate quickly in the face of minor infection, metabolic stress, or environmental changes. Physician should carefully review medications, reduce doses if possible, carefully search for infections, normalize patient environment, and introduce medications one at a time (Rogan and Lippa, 2002).

References

Aarsland, D., Litvan, I., Salmon, D., Galasko, D., Wentzel-Larsen, T., and Larsen, J. P. (2003). Performance on the dementia rating scale in Parkinson's disease with dementia and dementia with Lewy bodies: Comparison with progressive supranuclear palsy and Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatr.* **74**(9), 1215–1220.

Aarsland, D., Perry, R., Larsen, J. P., McKeith, I. G., O'Brien, J. T., Perry, E. K., Burn, D., and Ballard, C. G. (2005b). Neuroleptic sensitivity in Parkinson's disease and parkinsonian dementias. *J. Clin. Psychiatr.* **66**(5), 633–637.

Aarsland, D., Kurz, M., Beyer, M., Bronnick, K., Pippenstock, N., and Ballard, C. (2008). Early discriminatory diagnosis of dementia with Lewy bodies. The emerging role of CSF and imaging biomarkers. *Dement. Geriatr. Cogn. Disord.* **25**(3), 195–205.

American Psychiatric Association (2004). "Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR)." Vol 157, 4th ed., 3rd revision, American Psychiatric Association, Arlington, VA.

Baba, M., Nakajo, S., Tu, P. H., Tomita, T., Nakaya, K., Lee, V. M., Trojanowski, J. Q., and Iwatsubo, T. (1998). Aggregation of alpha-synuclein in Lewy bodies of sporadic Parkinson's disease and dementia with Lewy bodies. *Am. J. Pathol.* **152**(4), 879–884.

Ballard, C. G., Chalmers, K. A., Todd, C., McKeith, I. G., OBrien, J. T., Wilcock, G., Love, S., and Perry, E. K. (2007). Cholinesterase inhibitors reduce cortical Abeta in dementia with Lewy bodies. *Neurology* **68**(20), 1726–1729.

Barber, R., Panikkar, A., and McKeith, I. G. (2001). Dementia with Lewy bodies: Diagnosis and management. *Int. J. Geriatr. Psychiatr.* **16,** S12–S18.

Boeve, B. F., Silber, M. H., and Ferman, T. J. (2004). REM sleep behavior disorder in Parkinson's disease and dementia with Lewy bodies. *J. Geriatr. Psychiatr. Neurol.* **17**(3), 146–157.

Boeve, B. F., Silber, M. H., Saper, C. B., Ferman, T. J., Dickson, D. W., Parisi, J. E., Benarroch, E. E., Ahlskog, J. E., Smith, G. E., Caselli, R. C., Tippman-Peikert, M., *et al.* (2007). Pathophysiology of REM sleep behavior disorder and relevance to neurodegenerative disease. *Brain* **130**(Pt. 11), 2770–2788.

Burn, D. J., and McKeith, I. G. (2003). Current treatment of dementia with Lewy bodies and dementia associated with Parkinson's disease. *Mov. Disord.* **18**(Suppl. 6), S72–S79.

Burn, D. J., Rowan, E. N., Minett, T., Sanders, J., Myint, P., Richardson, J., Thomas, A., Newby, J., Reid, J., OBrien, J. T., and McKeith, I. G. (2003). Extrapyramidal features in Parkinson's disease with and without dementia and dementia with Lewy bodies: A cross-sectional comparative study. *Mov. Disord.* **18**(8), 884–889.

Connor, D. J., Salmon, D. P., Sandy, T. J., Galasko, D., Hansen, L. A., and Thal, L. J. (1998). Cognitive profiles of autopsy-confirmed Lewy body variant vs pure Alzheimer disease. *Arch. Neurol.* **55**(7), 994–1000.

Duda, J. E., Giasson, B. I., Mabon, M. E., Lee, V. M., and Trojanowski, J. Q. (2002). Novel antibodies to synuclein show abundant striatal pathology in Lewy body diseases. *Ann. Neurol.* **52**(2), 205–210.

Emre, M., Aarsland, D., Brown, R., Burn, D. J., Duyckaerts, C., Mizuno, Y., Broe, G. A., Cummings, J., Dickson, D. W., Gauthier, S., Goldman, J., Goetz, C., *et al.* (2007). Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov. Disord.* **22**(12), 1689–1707.

Fahn, S., and Elton, R. L., and UPDRS program members (1987). Unified Parkinson's disease rating scale. *In* "Recent Developments in Parkinsons Disease" (S. Fahn, C. D. Marsden, M. Goldstein, and D. B. Calne, Eds.), Vol. 2, pp. 153–163. Macmillan Healthcare Information, Florham Park, NJ.

Fantini, M. L., Ferini-Strambi, L., and Montplaisir, J. (2005). Idiopathic REM sleep behavior disorder: Toward a better nosologic definition. *Neurology* **64,** 780–786.

Hamilton, R. L. (2000). Lewy bodies in Alzheimer's disease: A neuropathological review of 145 cases using alpha-synuclein immunohistochemistry. *Brain Pathol.* **10**(3), 378–384.

Harding, A. J., and Halliday, G. M. (2001). Cortical Lewy body pathology in the diagnosis of dementia. *Acta Neuropathol.* **102,** 355–363.

Harding, A. J., Broe, G. A., and Halliday, G. M. (2002). Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. *Brain* **125**(Pt. 2), 391–403.

Janvin, C. C., Larsen, J. P., Salmon, D. P., Galasko, D., Hugdahl, K., and Aarsland, D. (2006). Cognitive profiles of individual patients with Parkinson's disease and dementia: Comparison with dementia with lewy bodies and Alzheimer's disease. *Mov. Disord.* **21**(3), 337–342.

Kramer, M. L., and Schulz-Schaeffer, W. J. (2007). Presynaptic alpha-synuclein aggregates, not Lewy bodies, cause neurodegeneration in dementia with Lewy bodies. *J. Neurosci.* **27**(6), 1405–1410.

Lippa, C. F., Fujiwara, H., Mann, D. M. A., Giasson, B., Baba, M., Schmidt, M. L., Nee, L. E., O'Connell, B., Pollen, D. A., St. George-Hyslop, P., Ghetti, B., Nochlin, D., *et al.* (1998). Lewy bodies contain altered alpha-synuclein in brains of many familial Alzheimer's disease patients with mutations in presenilin and amyloid precursor protein genes. *Am. J. Pathol.* **153,** 1365–1370.

Lippa, C. F., Smith, T. W., and Perry, E. (1999). Dementia with Lewy bodies: Choline acetyltransferase parallels nucleus basalis pathology. *J. Neural Transm.* **106,** 525–535.

Lippa, C. F., Schmidt, M. L., Trojanowski, J. Q., and Lee, V. M. Y. (2001). Alpha-synuclein and familial Alzheimer's disease: Epitope mapping parallels DLB and Parkinson's disease. *Arch. Neurol.* **58,** 1817–1820.

Lippa, C. F., Boeve, B. F., Parisi, J. E., and Keegan, B. M. (2007a). A 75-year-old man with cognitive impairment and gait changes. *Neurology* **69**(11), 1183–1189.

Lippa, C. F., Duda, J. E., Grossman, M., Hurtig, H. I., Aarsland, D., Boeve, B. F., Brooks, D. J., Dickson, D. W., Dubois, B., Emre, M., Fahn, S., Farmer, J. M., *et al.* DLB/PD-D Working Group (2007b). DLB and PD-D boundary issues: Diagnosis, treatment, molecular pathology, and biomarkers. *Neurology* **68**(11), 812–819.

McKeith, I. G., and Mosimann, U. P. (2004). Dementia with Lewy bodies and Parkinson's disease. *Parkinsonism Relat. Disord.* **10**(Suppl. 1), S15–S18.

McKeith, I., Fairbaim, A., Perry, R., *et al.* (1992a). Neuroleptic sensitivity in patients with senile dementia of Lewy body type. *BMJ* **305,** 673–678.

McKeith, I. G., Galasko, D., Kosaka, K., Perry, E. K., Dickson, D. W., Hansen, L. A., Salmon, D. P., Lowe, J., Mirra, S. S., Byrne, E. J., Lennox, G., Quinn, N. P., *et al.* (1996). Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies: Report of the consortium on DLB international workshop. *Neurology* **47**(5):1113–1124.

McKeith, I. G., Perry, R. H., Fairbairn, A. F., Jabeen, S., and Perry, E. K. (1992b). Operational criteria for senile dementia of Lewy body type (SDLT). *Psychol. Med.* **22,** 911–922.

McKeith, I., Mintzer, J., Aarsland, D., *et al.* (2004). Dementia with Lewy bodies. *Lancet Neurol.* **3,** 19–28.

McKeith, I. G., Dickson, D. W., Lowe, J., *et al.* (2005). Consortium on DLB. Diagnosis and management of dementia with Lewy bodies: Third report of the DLB Consortium. *Neurology* **65**(12), 1863–1872.

McKeith, I. G., Rowan, E., Askew, K., *et al.* (2006). More severe functional impairment in dementia with Lewy bodies than Alzheimer disease is related to extrapyramidal motor dysfunction. *Am. J. Geriatr. Psychiatr.* **14**(7), 582–588.

Mormont, E., Laurier-Grymonprez, L., Baisset-Mouly, C., and Pasquier, F. (2003). The profile of memory disturbance in early Lewy body dementia differs from that in Alzheimer's disease. *Rev. Neurol.* **159**(8–9), 762–766.

Mosimann, U. P., Rowan, E. N., Partington, C. E., Collerton, D., Littlewood, E., O'Brien, J. T., Burn, D. J., and McKeith, I. G. (2006). Characteristics of visual hallucinations in Parkinson's disease dementia and dementia with Lewy bodies. *Am. J. Geriatr. Psychiatry.* **14**(2),153–160.

Mukaetova-Ladinska, E. B., and McKeith, I. G. (2006). Pathophysiology of synuclein aggregation in Lewy body disease. *Mech. Ageing. Dev.* **127**(2),188–202.

O'Brien, J. T., Firbank, M. J., Mosimann, U. P., *et al.* (2005). Change in perfusion, hallucinations and fluctuations in consciousness in dementia with Lewy bodies. *Psychiatr. Res.* **139**(2), 79–88.

Perry, E. K., Haroutunian, V., Davis, K. L., *et al.* (1994). Neocortical cholinergic activities differentiate Lewy body dementia from classical Alzheimer's disease. *Neuroreport* **5,** 747–749.

Rajput, A., Dickson, D. W., Robinson, C. A., *et al.* (2006). Parkinsonism, Lrrk2 G2019S, and tau neuropathology. *Neurology* **67**(8), 1506–1508.

Rockenstein, E., Hansen, L., Mallory, M., *et al.* (2001). Altered expression of the synuclein family mRNA in Lewy body and Alzheimer's disease. *Brain Res.* **914,** 48–56.

Rogan, S., and Lippa, C. F. (2002). Alzheimer's disease and other dementias: A review. *Am. J. Alzheimers Dis. Other Demen.* **17**(1), 11–17.

Samuel, W., Galaski, D., Masliah, E., and Hanson, L. A. (1996). Neocortical Lewy body counts correlate with dementia in the Lewy body variant of Alzheimer's disease. *J. Neuropathol. Exp. Neurol.* **55,** 44–52.

Samuel, W., Caligiuri, M., Galasko, D., *et al.* (2000). Better cognitive and psychopathologic response to donepezil in patients prospectively diagnosed as dementia with Lewy bodies: A preliminary study. *Int. J. Geriatr. Psychiatr.* **15,** 794–802.

Schiesling, C., Kieper, N., Siedel, K., and Kruger, R. (2008). Review: Familial Parkinson's disease—Genetics, clinical phenotype and neuropathology in relation to the common sporadic form of the disease. *Neuropathol. Appl. Neurobiol.* **34**(3), 255–271.

Walker, Z., Allen, R. L., Shergill, S., and Katona, C. L. (1997). Neuropsychological performance in Lewy body dementia and Alzheimer's disease. *Br. J. Psychiatr.* **170,** 156–158.