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DEMENTIA WITH LEWY BODIES

IAN G. MCKEITH
DAVID BURN
JOHN O'BRIEN
ROBERT PERRY
ELAINE PERRY

The concept of dementia with Lewy bodies (DLB) has been slowly gaining momentum since 1961, when Okazaki et al. (1) published case reports about two male patients, ages 69 and 70 years, who presented with dementia and died shortly thereafter with severe extrapyramidal rigidity. Autopsy showed Lewy body pathology in the cerebral cortex. During the next 20 years, a total of 34 such cases was reported, all by Japanese workers, who adopted the term *diffuse Lewy body disease* to describe the typical distribution of Lewy bodies in subcortical and cortical regions (2).

During the following decade, cortical Lewy body pathology was found in up to 20% of all cases of elderly demented patients reaching autopsy (3–5), and in 1990, Hansen et al. (6) reported that 36% of patients given a clinical diagnosis of Alzheimer disease (AD) had Lewy bodies at autopsy—the Lewy body variant of AD (6). The significance of these reports was unclear—whether this was a new type of dementing disorder that had not previously existed, or whether the Lewy bodies had previously been overlooked. Reexamination of original material from a cohort of autopsy material collected during the 1960s in Newcastle upon Tyne revealed that 17% of the cases had cortical Lewy bodies, a prevalence similar to that found today. It appears, then, that DLB is not a new disorder but is one that has only recently been recognized, even though it is the second most common form of degenerative dementia in old age, only AD being more common.

Lewy bodies are spherical, intracytoplasmic, eosinophilic, neuronal inclusions; they have a dense hyaline core and a halo of radiating filaments composed of abnormally truncated and phosphorylated intermediate neurofilament proteins that include ubiquitin and associated enzymes. They were first described by the German neuropathologist Friederich Lewy when he was working in Alzheimer's laboratory in Munich between 1910 and 1912. Subcortical Lewy bodies are easily seen with conventional hematoxylin and eosin staining. The presence of Lewy bodies in pigmented brainstem nuclei (the substantia nigra in particular), coupled with neuronal loss and gliosis, comprise the characteristic pathologic findings in the prototypal Lewy body disease, which is Parkinson disease (PD).

Cortical Lewy bodies lack the characteristic core and halo appearance of their brainstem counterparts and were therefore difficult to detect until the late 1980s, when the development of anti-ubiquitin immunocytochemical staining methods allowed their true prevalence to be appreciated (4). More recently, α-synuclein antibodies have been shown to label purified Lewy bodies, and the α-synuclein antibodies PER1 and PER2 strongly stain Lewy bodies and Lewy neurites (7,8) (Fig. 91.1). Axon pathology in DLB involves not only α-synuclein but also β- and γ-synucleins (9). α-Synuclein antibodies reveal presynaptic axon pathology in various regions of the hippocampus, and γ-synuclein antibodies detect axonal spheroid-like inclusions in the dentate molecular layer.

Current opinions on the classification of Lewy body disorders is that a spectrum of disease exists, with the clinical presentation varying according to the site of Lewy body formation and neuronal loss (10) (Table 91.1). Although ''pure'' presentations are seen in clinical practice, heterogenous combinations of parkinsonism, dementia, and signs of autonomic failure are most frequent. Recommendations have recently been made as to which brain regions should be examined for Lewy bodies, and a simple, semiquantitative scoring system has been devised in which a score of 1 is assigned if any Lewy bodies are seen in a given area and a score of 2 if more than five are seen per field (11). These

Ian G. McKeith and John O'Brien: Institute for the Health of the Elderly, Wolfson Research Centre, Newcastle General Hospital, Newcastle upon Tyne, United Kingdom.

David Burn: Department of Neurology, Regional Neurosciences Centre, Newcastle upon Tyne, United Kingdom.

Robert Perry: Department of Neuropathology, Newcastle General Hospital, Newcastle upon Tyne, United Kingdom.

Elaine Perry: MRC Neurochemical Pathology Unit, Newcastle General Hospital, Newcastle upon Tyne, United Kingdom.

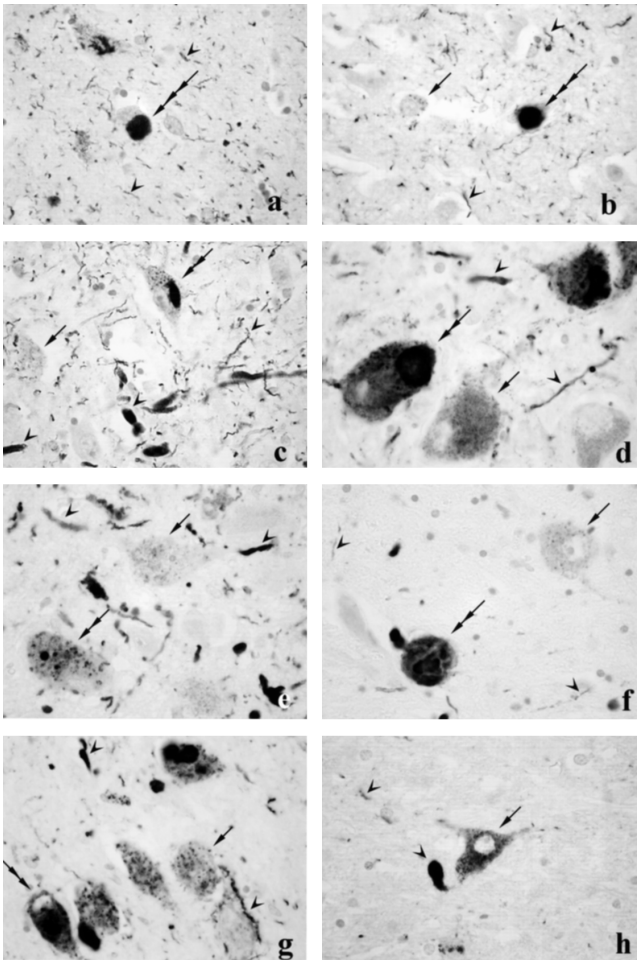

FIGURE 91.1. Examples of α-synuclein pathology from cases with Parkinson disease or dementia with Lewy bodies. Immunohistochemistry was performed with α-synuclein monoclonal antibodies from Novocastra Laboratories on formalin-fixed, paraffin-embedded sections pretreated with formic acid, Vectastain Elite ABC peroxidase kit, diaminobenzidine tetrahydrochloride (DAB), and hematoxylin counterstain. *Single arrow,* granular neuronal inclusions. *Double arrow,* combined granular and solid irregular neuronal inclusions. *Triple arrow,* Lewy body-like neuronal inclusions. *Arrowhead,* thin and thick neurites. Original magnification of A through H was ×63. **A:** Transentorhinal cortex. **B:** Anterior cingulate cortex. **C:** Hippocampus, CA2 segment. **D:** Substantia nigra in lower midbrain. **E:** Dorsal raphe in lower midbrain. **F:** Pedunculopontine nucleus in lower midbrain. **G:** Nucleus basalis of Meynert. **H:** Thalamus, central lateral nucleus.

TABLE 91.1. PRIMARY LEWY BODY DISORDERS

Region Primarily Affected	Clinical Syndrome	Classification
Substantia nigra	Extrapyramidal movement disorder	Parkinson disease
Limbic cerebral cortex	Cognitive decline and neuropsychiatric symptoms	Dementia with Lewy bodies
Sympathetic neurons in spinal cord	Autonomic failure	Primary autonomic failure
Dorsal vagal nuclei	Dysphagia	Lewy body dysphagia
Pedunculopontine nucleus[a]	Sleep disturbance	REM sleep behavior disorder

REM, rapid eye movement.
[a]Precise clinicopathologic correlate for this is yet to be established, although involvement of the pedunculopontine nucleus is highly probable from current data.
Adapted from Lowe JS, Mayer RJ, Landon M, Pathological significance of Lewy bodies in dementia; In: Perry R, McKeith I, Perry E, eds. *Dementia with Lewy bodies*. New York: Cambridge University Press, 1996:195–203.

scores are then added to generate three possible pathologic categories—brainstem-predominant, limbic (or transitional), and neocortical DLB. It has not yet been established to what extent these three patterns of pathologic distribution correlate with different clinical profiles. Extensive neocortical pathology is not necessary for the development of dementia or other psychiatric symptoms, all of which may occur in the presence of limbic disease alone.

A heated debate has surrounded the interpretation of the Alzheimer-type changes that are also seen in most patients with DLB. Numerous senile plaques are found in most, although these are morphologically indistinguishable from those of pure AD (12). Two reports have appeared of a relative sparsity of β-amyloid proteins 1 through 40 in DLB in comparison with AD (13,14). However, the plaques are seldom tau-immunoreactive, and indeed in 80% to 90% of cases of DLB, no evidence of significant neocortical tau pathology, paired helical filaments, or neurofibrillary tangles can be found (15). Whether or not DLB is considered to be a variant of AD depends on the pathologic definition of AD used (16). Thus, 77% of cases with Lewy body pathology and dementia had ''plaque-only'' AD, a concept derived from definitions of AD that depend heavily on plaque density. By contrast, 80% to 90% of DLB cases failed to fulfill definitions of AD that require numbers of neocortical neurofibrillary tangles above a certain threshold (17). The new NIA/Reagan Foundation criteria for AD appear to be responsible for a significant shift in this direction, with a proposed requirement for frequent neurofibrillary tangles equivalent to Braak stages 5 and 6 (18). DLB and pure AD are, according to such criteria, pathologically distinct in the majority of cases. Gomez-Isla et al. (19) recently concluded that the lack of a relationship between the extent of Alzheimer-type changes and Lewy body formation in DLB suggests that DLB is a distinct disease rather than a variant of AD.

In summary, at least three anchor points appear to be recognizable along a spectrum of neurodegenerative disorders. PD is a disorder of predominantly subcortical Lewy body neurofilament inclusions, which are the most visible markers of an extensive neuritic degeneration involving α-synuclein and ubiquitin. A more extensive distribution of Lewy bodies typifies DLB, in which significant β-amyloidosis and senile plaque formation that fall short of what is seen in AD are also usually present. AD, in contrast, is characterized by a combination of β-amyloidosis and neocortical neurofibrillary tangles—the latter representing dysregulation of microtubule assembly proteins—tau-related cytoskeletal abnormalities that are not found in most cases of DLB.

Alzheimer disease and DLB do share the features of β-amyloidosis, senile plaque formation, and severe depletion of acetylcholine, which is even greater in DLB than in AD. Interestingly, they both also share an increased frequency of apolipoprotein e4 allele (20), which is not seen in nondemented cases of PD. Additional vascular changes are seen in up to 30% of cases of AD and DLB.

CLINICAL FEATURES

Most cases of DLB coming to autopsy are men (21–29). Although the mean age at onset and survival are similar to those in AD, survival times in DLB are sometimes skewed by rapidly progressive illness. The reduction in survival is probably partly attributable to neuroleptic sensitivity reactions (23). More recently, no differences in age at onset or survival were reported by Heyman et al. (30) and Walker et al. (31) between 24 and 32 patients with DLB and 74 and 43 patients with AD, respectively, although cognitive decline appeared to be faster in DLB (32).

Dementia is usually, but not always, the presenting feature of DLB; a minority of patients present with psychosis in the absence of dementia, some with mood disorders or psychosis, and others with orthostatic hypotension and falls. Fluctuation occurs in half to three-fourths of patients, but the range reported is wide, probably because this is such a difficult symptom to define. Fluctuation, irrespective of definition, is not commonly seen in AD. Visual hallucinations are present in one-third to one-half of DLB patients, although in some series the prevalence is 80%. Auditory hallucinations may occur in 20% of DLB subjects but seldom in AD. Depressive symptoms are common in both disorders, but a 38% prevalence in DLB is significantly greater than that in AD and similar to the rates reported in PD. Shimomura et al. (33) reported disproportionately more severe visuoperceptual, visuoconstructive, and visuospatial dysfunction and disproportionately milder impairment of memory. Ballard et al. (34) reported that although recent memory function is better preserved, visuospatial praxis is more impaired, a finding that potentially provides a psychological tool for differentiating DLB from AD.

A history of bursts of vigorous movements of the arms and legs with vocalization during sleep and associated with dream recall is highly suggestive of rapid-eye-movement (REM) sleep behavior disorder. Although REM sleep disorder may occur in, or indeed precede, a range of neurodegenerative disorders, including PD and multiple-system atrophy, in the context of degenerative dementia it suggests DLB (35).

The reported frequency of extrapyramidal signs in DLB varies greatly. Furthermore, the presence of extrapyramidal signs in DLB and their value in discriminating DLB from AD is unresolved. A number of issues must be considered in this context. First, the ''background'' population prevalence of parkinsonism is very common in the age range in which both DLB and AD occur. In one recent community-based study of 467 residents, parkinsonism (defined as the presence of at least two of the following: bradykinesia, gait disturbance, rigidity and tremor) was found to affect nearly

15% of people 65 to 74 years of age, 30% of those 75 to 84, and 52% of those 85 and older (36). Second, a wide range of frequencies (5% to 90%) of extrapyramidal signs has been reported in patients with AD (37). Although this may be related in part to differences in disease severity and study duration, it also likely reflects imprecision in the clinical definition of so-called extrapyramidal signs. Thus, predominantly cortically determined signs, such as ideomotor apraxia, paratonic rigidity (Gegenhalten), and frontal gait disorder, may be mistaken for bradykinesia, parkinsonian rigidity, and parkinsonian gait, respectively. Such motor disturbances produce "pseudoparkinsonism," which is fundamentally different from the true parkinsonism determined by basal ganglia pathology (38). Finally, the reported rates for parkinsonism in DLB undoubtedly partly reflect case ascertainment biases. Patients collected through neurologic departments, which primarily receive referrals for movement disorders, are more likely to exhibit extrapyramidal signs than are DLB cases identified through memory clinics and psychogeriatric services.

Overall, probably fewer than half of DLB cases have extrapyramidal signs at presentation, and a fourth continue to have no evidence of them throughout their illness. Clinicians must therefore be prepared to diagnose DLB in the absence of parkinsonism—if they do not, their case detection rates will be unacceptably low.

When extrapyramidal signs do occur in DLB, a number of studies have contrasted them with the signs in PD in an attempt to characterize parkinsonian syndrome and identify potential diagnostic markers for DLB (39,40). In comparison with PD, less resting tremor and myoclonus, greater disease symmetry (especially at presentation), and a poor response to levodopa have all been reported for DLB, albeit inconsistently. It should be emphasized that any differences reported reflect group differences. The positive predictive value of any particular sign, or combination of signs, in differentiating DLB from PD in an individual patient has not been established. In common with PD, rigidity and bradykinesia, hypophonic speech, masked facies, stooped posture, and festinant gait have all been reported for DLB.

Finally, recurrent falls affect up to a third of DLB cases, a proportion significantly greater than in AD, as does neuroleptic sensitivity, detected in 61% of all DLB patients who receive neuroleptics but in only 15% of AD patients. Two studies have examined interrater reliability and found agreement rates and κ values to be acceptable for some symptoms of DLB, such as delusions, hallucinations, parkinsonism, and falls, but unacceptably low for others, particularly fluctuation (41,42).

The recent consensus criteria for the clinical diagnosis of DLB are shown in Table 91.2 (11). Emphasis is placed on the particular characteristics of the dementia syndrome—attentional deficits and prominent frontal–subcortical and visuospatial dysfunction. Fluctuation is no longer essential for the diagnosis, although it is frequently present. It seems probable that the fluctuating attentional deficit is linked to dysregulation of central cholinergic mechanisms controlling the level of consciousness (see section below on neurochemical clinical–pathologic relationships). The important hallucinatory symptoms are specified as visual, recurrent, and detailed, usually occurring most days of the week; they are typically colorful, three-dimensional images of animals and children. Insight into the unreal nature of these hallucinations is usually absent while they occur but is gained after the event. Ballard et al. (43) reported that more than 90% of patients with DLB experience such hallucinations and that in comparison with those of AD, the hallucinations are more persistent and the images are more likely to be accompanied by vocalization. Spontaneous parkinsonism not attributable to medication is a key symptom in most patients with DLB. If two of these three symptoms (fluctuations, visual hallucinations, and parkin-

TABLE 91.2. CONSENSUS CRITERIA FOR THE CLINICAL DIAGNOSIS OF *PROBABLE* AND *POSSIBLE* DEMENTIA WITH LEWY BODIES

Consensus criteria for the clinical diagnosis of *probable* and *possible* dementia with Lewy bodies (DLB)

1. The central feature required for a diagnosis of DLB is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or presistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and of frontal–subcortical skills and visuospatial ability may be especially prominent.
2. Two of the following core features are essential for a diagnosis of *probable* DLB; one is essential for *possible* DLB.
   a. Fluctuating cognition with pronounced variations in attention and alterness
   b. Recurrent visual hallucinations that are typically well formed and detailed
   c. Spontaneous motor features of parkinsonism
3. Features supportive of the diagnosis are the following:
   a. Repeated falls
   b. Syncope
   c. Transient loss of consciousness
   d. Neuroleptic sensitivity
   e. Systematized delusions
   f. Hallucinations in other modalities
   (Depression and REM sleep behavior disorder have been suggested as additional supportive features.)
4. A diagnosis of DLB is less likely in the presence of
   a. Stroke disease, evident as focal neurologic signs or on brain imaging
   b. Evidence on physical examination and investigation of any physical illness, or other brain disorder, sufficient to account for the clinical picture

DLB, dementia with Lewy bodies; REM, rapid eye movement.
Adapted from McKeith IG, Galasko D, Kosaka K et al., Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* 1996;47:1113–1124.

TABLE 91.3. AUTOPSY VALIDATION OF CONSENSUS CRITERIA FOR DEMENTIA WITH LEWY BODIES

	Sensitivity	Specificity
Mega et al., 1996 (41)	0.75	0.79
Litvan et al., 1998 (116)	0.18	0.99
Papka et al., 1998 (117)	0.43	—
McShane et al., 1998[a] (45)	0.70	0.89
Holmes et al., 1999 (118)	0.22	1.00
Luis et al., 1999 (119)	0.57	0.90
Lopez et al., 1999 (120)	0.00	1.00
Verghese et al., 1999 (121)	0.61	0.84
McKeith et al., 2000[a] (122)	0.83	0.95

[a]Clinical diagnoses made prospectively, not by chart review.

sonism) are present, a diagnosis of probable DLB is made; if only one is present, a diagnosis of possible DLB is allowed.

The sensitivity and specificity of the consensus clinical criteria against autopsy findings have been examined in several studies (Table 91.3). All find the diagnostic specificity to be relatively high, comparable with that of existing clinical criteria for AD and PD. This high specificity suggests that the DLB clinical criteria are appropriate for confirmation of the diagnosis (few false-positives). Sensitivity of case detection is reported as more variable and generally lower. The tendency to clinical underdiagnosis was noted during the second international workshop on DLB (44). However, two studies prospectively applying consensus criteria (as opposed to retrospective inspection of previous case records) did detect more than 80% of autopsy-confirmed DLB cases (45,46). A prospective validation study in Newcastle reported on a sample of 50 hospital-referred demented cases followed to autopsy (46). The sensitivity and specificity for a clinical diagnosis of probable DLB were 0.83 and 0.95, respectively.

DIFFERENTIAL DIAGNOSIS

Four main categories of disorders should be considered in the differential diagnosis of DLB. These are the following:

1. Other dementia syndromes. Sixty-five percent of autopsy-confirmed DLB cases meet the NINCDS/ADRDA clinical criteria for probable or possible AD (47), which is the most frequent clinical misdiagnosis applied to patients with DLB presenting with a primary dementia syndrome. For this reason, DLB should routinely be excluded when a diagnosis of AD is made. Up to a third of DLB cases are additionally misclassified as vascular dementia on the Hachinski ischemic index by virtue of the fluctuating nature and course of the illness. However, pyramidal and focal neurologic signs are usually absent. The development of myoclonus in patients with a rapidly progressive form of DLB may lead the clinician to suspect sporadic Creutzfeldt–Jakob disease (11).

2. Other causes of delirium. In patients with intermittent delirium, appropriate examination and laboratory tests should be performed during the acute phase to maximize the chances of detecting infective, metabolic, inflammatory, or other etiologic factors. Pharmacologic causes are particularly common in elderly patients. Although the presence of any of these features makes a diagnosis of DLB less likely, comorbidity is not unusual in elderly patients, and the diagnosis should not be excluded simply on this basis.

3. Other neurologic syndromes. In patients with a prior diagnosis of PD, the onset of visual hallucinations and fluctuating cognitive impairment may be attributed to side effects of antiparkinsonian medications, and this possibility must be tested by dose reduction or withdrawal. Other neurodegenerative akinetic–rigid syndromes associated with a poor response to levodopa, cognitive impairment, and postural instability include progressive supranuclear palsy, corticobasal degeneration, and progressive subcortical gliosis. Normal-pressure hydrocephalus must be considered in a patient with so-called lower-body parkinsonism, cognitive impairment, and urinary incontinence. Syncopal episodes in DLB are often incorrectly attributed to transient ischemic attacks despite an absence of focal neurologic signs. Recurrent disturbances in consciousness accompanied by complex visual hallucinations may suggest complex partial seizures (temporal lobe epilepsy), and vivid dreaming with violent movements during sleep may meet the criteria for REM sleep behavior disorder. Both these conditions have been reported as uncommon presenting symptoms of autopsy-confirmed DLB. Patients with REM sleep behavior disorder differ clinically from those without, performing worse on attentional tasks (48).

4. Other psychiatric disorders. If parkinsonian features or cognitive decline develops spontaneously in a patient, or if a patient shows excessive sensitivity to neuroleptic medication in the course of late-onset delusional disorder, depressive psychosis, or mania, the diagnosis of DLB should be considered.

NEUROTRANSMITTER ABNORMALITIES

Neurochemical activities have been widely investigated in AD and PD, including in some instances PD with dementia, but fewer reports are available on DLB. These are summarized in Table 91.4 as they relate to neurotransmitter systems.

Reductions in presynaptic cholinergic activities, particularly in the cerebral neocortex, are more marked in DLB than in AD and are similar to those in PD with dementia (49). As in PD, the cortical cholinergic deficit appears to reflect neuronal loss in the basal nucleus of Meynert (50).

TABLE 91.4. NEUROTRANSMITTER ACTIVITIES IN DLB, AD, AND PD[a]

	DLB	AD	PD
I. CHOLINERGIC SYSTEM			
ChAT			
Cerebral cortex	↓↓	↓	↓↓[b]
Hippocampus	↓	↓↓	↓
Striatum	↓	↓	→
Thalamus	↓	→/↓	→
AChE			
Cortex	↓	↓	↓
BUChE			
Cortex		↓	
VAChT			
Cortex		↓	↓[b]
Muscarinic receptors			
M1			
Cortex	↑	→	↑[b]
Striatum	↓	↑	→
M2			
Cortex		↓	
Nicotinic receptors			
α7/αBT binding			
Cortex	→	→	
Thalamus	↓	↓	
α4/high-affinity agonist site			
Cortex	↓	↓	↓
Striatum	↓	→/↓	↓↓
Thalamus	→/↓	→/↓	→
II. MONOAMINERGIC SYSTEMS			
DOPAMINERGIC			
Presynaptic			
Dopamine			
Striatum	↓	→	↓↓
Cortex	↓	→	↓
Dopamine transporter[c]	↓	→	↓↓
Receptors			
D1 receptor[c]	→		→
D2 receptor[c]	↑	→	→/↓
D3 receptor[c]	→/↓		→
SEROTONINERGIC			
Presynaptic			
Serotonin			
Striatum	↓		↓
Cortex	↓	↓	↓
Serotonin transporter			
Cortex	↓	↓	↓
Receptors			
5-HT_{2A} receptor			
Cortex	→/↓	↓	↓
NORADRENERGIC			
Noradrenaline			
Striatum	↓		↓↓
Cortex		↓	
MAO-B		↑	

5-HT, 5-hydroxytryptamine; AChE, acetylcholinesterase; AD, alzheimer disease; BUChE, butyrycholinesterase; ChAT, choline acetyltransferase; DLB, dementia with Lewy bodies; MAO-B, monoamineoxidase B; PD, Parkinson disease; VAChT, vesicular acetylcholine transporter.

[a]Summary of neurochemical findings, reviewed Perry et al. (123); see also the following recent references: 51,54,56,59,124,125.

[b]Denotes more extensive in PD + dementia.

[c]Striatal activities.

The cortical cholinergic pathology is independent of the extent of Alzheimer pathology, being equally great in DLB cases with and without this type of pathology (51). Cholinergic deficits in DLB extend beyond the cortex to the striatum and certain nuclei of the thalamus (52). Also, in contrast to AD and similar to PD with dementia, DLB is associated with elevation of the muscarinic receptor subtype M1 (53), a finding that has recently been confirmed by immunoabsorption studies (54). However, muscarinic M1 receptors are not uncoupled to the same extent as in AD (52; Perry et al., *in preparation*). Changes in nicotinic receptors in the cortex include a loss of the high-affinity agonist binding site (likely to reflect the α_4 subunit), but no change in the α_7 subunit or α-bungarotoxin binding (54a). In contrast, little change in nicotine binding occurs in the thalamus, but highly significant reductions in α-bungarotoxin binding are seen in the reticular nucleus (55). Similar nicotinic receptor abnormalities occur in AD and (as far as has been investigated) in PD, although the loss of nicotine binding in the striatum is greater in PD, in keeping with the more extensive reduction in basal ganglia dopaminergic projections (56). Although the loss of high-affinity nicotinic receptor binding in AD has been related to synapse loss, measured by synaptophysin levels (57), synaptophysin loss occurs in DLB only when the pathology includes the Alzheimer type (58).

The involvement of the dopaminergic system is the other consistent neurochemical feature of DLB (Table 91.4); however, as might be expected from the variations in extrapyramidal features (absent/mild to severe, as in classic PD), the extent of dopamine or dopamine transporter loss in the striatum varies widely. Earlier reports that dopamine loss was in some cases severe despite the absence of neurologic symptoms (49), a finding that was interpreted to indicate compensatory striatal pathology, need to be replicated in prospectively assessed cases because symptoms may have been overlooked in psychogeriatric clinics; furthermore, neuroleptic medication reduces striatal dopamine. Although in PD striatal dopamine deficits are more marked in caudal regions, particularly putamen, in DLB the loss of dopamine transporter is similar at different rostral caudal levels (59). Whereas in PD dopamine D2 receptors are up-regulated, at least in earlier stages of the disease, receptors are not increased in DLB and in particular are not up-regulated as a result of neuroleptic medication (60). In addition to striatal dopamine deficits, dopamine losses in cortical areas also occur (Table 91.4).

The significance of the serotoninergic, noradrenergic, and neuropeptide (e.g., somatostatin and corticotropin-releasing factor) abnormalities that occur in DLB, as in AD and PD, has not generally been evaluated in pathologic or clinical terms. The clinical significance of some of the cholinergic abnormalities that have so far been examined in prospectively assessed cases is discussed in the section on clinical–pathologic relationships.

GENETICS

Familial cases of DLB have been reported, although the majority of cases appear to be sporadic. Following the discovery of two separate missense mutations in the α-synuclein gene on chromosome 4 in a small number of families with pathologically confirmed early-onset PD, mutation screening was undertaken in this gene in both familial and sporadic cases of DLB (61). These studies failed to reveal any nucleotide changes within the exons screened.

Although, like cases of PD, most cases of DLB appear to be sporadic, this does not exclude a potentially significant genetic influence in the etiology of either condition. Such an influence may be via so-called susceptibility genes. Because DLB shares pathologic overlap with PD and AD, susceptibility genes of interest for both conditions have been considered in candidate gene approaches. For PD and DLB, allelic frequencies of the cytochrome P-450 gene *CYP2D6* (debrisoquine-4-hydroxylase) have been examined. The results of these studies have been conflicting. An increased frequency of the *CYP2D6*B* allele has been reported in DLB (62), whereas another study found no association (63). Others found no difference between the frequency of this allele in AD and DLB despite an increased frequency in PD (64). The current balance of evidence suggests that the *CYP2D6*B* allele is not a major genetic determinant of DLB.

The ϵ4 type of apolipoprotein E is significantly elevated in both DLB and AD, with a concomitant reduction in the Eϵ3 type of apolipoprotein. Interestingly, although the ϵ4 allele was associated with an increased risk for the development of DLB, it did not appear to affect the burden of pathology, measured by senile plaque and neurofibrillary tangle density in the neocortex (65). In AD, the ϵ4 allele is associated with neuronal loss in the substantia nigra (66). In PD, the ϵ4 allele increases the risk for drug-induced hallucinations (67).

Most recently, a significant difference has been reported for the allelic distribution of a pentanucleotide repeat within the promoter region of the nitric oxide synthase gene *(NOS2A)* in a comparison of autopsy-proven DLB cases with controls (68). Nitric oxide functions normally in the brain as a physiologic neuronal mediator, but excessive production of nitric oxide (e.g., after ischemic brain injury) can cause cell death through the generation of potent oxidants. Furthermore, with use of a murine MPTP model of parkinsonism, it has been shown that inhibitors of nitric oxide synthase may provide protective benefit in the treatment of PD (69).

Associations between polymorphisms within the α_2-macroglobulin, α_1-antichymotrypsin, and presenilin 1 genes and DLB have not been demonstrated (after accounting for apolipoprotein E ϵ4 allele frequency) (70–72).

Accumulating evidence suggests that patients with DLB are more responsive to cholinergic therapy than those with AD at a similar stage of dementia. The polymorphism causing the K allele in the gene for butyrylcholinesterase has been reported to be associated with AD, although this finding has not been replicated by others. In DLB, an increased number of butyrylcholinesterase K homozygotes have been found. It has been suggested that this genotype may partly explain the enhanced responsiveness to cholinesterase inhibitors in DLB (73). Although abnormalities in butyrylcholinesterase are evident in AD, including elevated enzymatic activity associated with both amyloid plaques and neurofibrillary tangles, the enzyme has not been examined in DLB.

CLINICAL–PATHOLOGIC RELATIONSHIPS

Cognitive and Neuropsychiatric

In DLB, a consistent gradient of LB density has been noted, as follows: substantia nigra > entorhinal cortex > cingulate gyrus > insula > frontal cortex > hippocampus > occipital cortex. Paralimbic and neocortical LB densities are highly correlated with each other but not with nigral pathology, which suggests that DLB should not be considered merely a severe form of PD (74). One study of pathologic burden versus clinical severity examined correlations between two simple measures of cognitive ability and a range of lesion counts and neurochemical measures in the midfrontal cortex of DLB cases (75). Severity of dementia was significantly correlated with LB density, plaque density, and severity of cholinergic deficit, but not with neurofibrillary tangle density or synaptophysin levels. In contrast, in AD cases, tangle density and synaptophysin levels were most highly correlated with clinical severity. This suggests that the dementias of DLB and AD may have different pathologic but similar neurochemical substrates. Other studies have failed to find robust correlations between LB density and clinical features (74,76).

Neurologic

Cell loss in the ventrolateral tier of the substantia nigra is the dominant pathologic correlate for parkinsonism in both DLB and PD. This is associated with gliosis and Lewy body formation. Dopaminergic neurons in this area of the substantia nigra project predominantly to the putamen, which, in turn, is an integral component of the so-called basal ganglia "motor loop" (77). The net effect of loss of the modulating effects of dopamine within the putamen is increased neuronal activity in the globus pallidus (internal segment). Because output from the globus pallidus (internal segment) is inhibitory to the ventrolateral thalamic nucleus, this leads to excessive inhibition of thalamic activity and thus reduced feedback to the motor cortex. The perturbation in this loop, resulting from dopamine deficiency, is believed to be the basis of the neural substrate for bradykinesia.

Although systematic studies have not yet been per-

formed, some evidence suggests that responsiveness to levodopa in DLB may be less than that in PD. Because the presynaptic lesion is similar in the two disorders, the answer may therefore lie postsynaptically. Evidence to support this notion comes from postmortem neurochemical studies comparing dopaminergic activities in DLB with those in PD and AD (59). In these studies, dopamine D2 receptor binding was reduced in the caudal putamen and was significantly lower than in PD at all levels.

Although the increased falls reported in DLB may be multifactorial, it is likely that more widespread involvement of brainstem nondopaminergic nuclei is a contributing factor. Degeneration of the predominantly cholinergic pedunculopontine nucleus is a likely explanation because neuronal loss in this structure has been associated with postural instability (78). In addition, degeneration of the pedunculopontine nucleus has been implicated as the pathophysiologic basis for REM sleep behavioral disorder, which is also reported in DLB (79).

Neurochemical

As yet, only a few clinical–neurochemical relationships have been identified in DLB. In earlier reports of the loss of cholinergic activity from the cortex, correlations were identified, as in AD, with the severity of cognitive impairments (17,75).

In regard to noncognitive or neuropsychiatric symptoms, patients with visual hallucinations have significantly lower levels of choline acetyltransferase than do nonhallucinators (80); recently, they have also been found to have lower levels of nicotinic α-bungarotoxin receptor binding in visual association cortex (Ballard et al., *in preparation*). Muscarinic M1 binding in temporal cortex is increased in patients experiencing persistent delusions (81). Delusional misidentification has also been associated with lower levels of α-bungarotoxin binding in this region (Ballard et al., submitted). Disturbances in consciousness are associated with a tendency for choline acetyltransferase to be lower in the thalamic reticular nucleus (53) and with a relative preservation of the high-affinity nicotinic receptor in the cortex (Ballard et al., submitted). Although reductions in this receptor correlate with attentional deficits, it appears that the ability to return periodically to normal levels of consciousness (fluctuations) depends on a degree of integrity of the nicotinic receptor. It has been suggested that greater EEG slowing is related to the greater cholinergic deficit in DLB than in AD (82). A hypothesis relating the function of cerebral acetylcholine in the integrative processes that generate conscious awareness has recently been proposed (83).

In regard to noncholinergic transmitter abnormalities, sensitivity to neuroleptic medication has been related to a lack of dopamine D2 receptor up-regulation, and depression to relatively preserved serotonin transporter levels (Ballard et al., submitted).

CLINICAL INVESTIGATIONS

As with any patient presenting with cognitive impairment, obtaining a full history and performing a mental and physical examination are essential steps toward making a firm clinical diagnosis. As with suspected cases of AD, the level and extent of laboratory investigations vary according to the clinical picture, associated comorbidity, and physical examination findings. However, because of the particular associations of DLB with fluctuations in attention and cognition and visual hallucinations, both very commonly associated with a variety of other organic disorders, the investigation of a suspected case of DLB requires a very careful laboratory evaluation. This usually includes routine hematology and biochemistry, determinations of erythrocyte sedimentation rate and creatine phosphate, thyroid function tests, measurements of B_{12} and folate levels, syphilis serology, and urinalysis. A chest roentgenogram may also be considered routine in view of the high incidence of lung carcinomas in the elderly, especially smokers. As in the diagnosis of AD, neuroimaging investigations are often helpful, both in excluding other intracranial disorders (including cerebrovascular disease) that may be responsible for the cognitive impairment and in providing supportive features for the diagnosis.

The EEG findings may be abnormal in up to 90% of DLB patients; loss of alpha rhythm and transient slow-wave activity in the temporal lobe areas are the most common changes (82). Patients with AD are less likely to have transient slow waves, and slowing of the dominant rhythm is less marked. However, the positive predictive value of the EEG in suspected cases of DLB has not been assessed in a prospective clinicopathologic study. Increasingly, some form of structural imaging is becoming essential to apply diagnostic criteria rigorously, such as the NINCDS/ADRDA criteria for AD, the NINCS/ADRDA criteria for vascular dementia, and the consensus criteria for DLB.

Structural Imaging Changes

Few studies have investigated computed tomographic (CT) or magnetic resonance imaging (MRI) changes in DLB. In a longitudinal study of AD subjects who came to postmortem examination, Förstl et al. (24) reported more pronounced frontal lobe atrophy on CT in eight subjects with LB pathology in a comparison with pure AD cases. However, using MRI, Harvey et al. (84) found no differences in frontal lobe volumes between AD and DLB subjects, a finding replicated in a different and larger cohort by Barber et al. (85). Although further studies are awaited, frontal lobe atrophy does not seem to be a particular feature of DLB. Similarly, DLB does not seem to differ from AD in terms of degree of ventricular enlargement or presence of white matter changes on MRI (86).

The strong association between AD and atrophy of the

medial temporal lobe, whether assessed by a linear measurement of medial temporal lobe width on CT (87) or visual or volumetric ratings of hippocampal atrophy on MRI (88, 89), led to an investigation of whether similar changes are associated with DLB. Jobst et al. (87) found medial temporal lobe atrophy of similar magnitude to that in AD in two of their four cases of DLB. However, with the use of MRI, both case reports and controlled studies have shown DLB to be associated with relative preservation of temporal lobe structures in comparison with AD (84,85,90,91). Volumetric analysis of subregions within the temporal lobe indicates that the differences lie in medial temporal lobe structures (i.e., hippocampus and parahippocampal gyrus) rather that in the lateral temporal lobe, which does not show any differences between AD and DLB. Volumetric analysis, although essential for research studies and investigating clinical correlates, is currently too time-consuming to be adopted into routine clinical practice. Using visual ratings, which can be performed quickly (1 minute per scan) and simply, Barber et al. (85) found that 38% of DLB subjects but no AD subjects had a normal rating of temporal lobe atrophy, which suggests that at least in some cases relative preservation of the hippocampus and medial temporal lobe may support a diagnosis of DLB. Sample medial temporal lobe images are shown in Fig. 91.2. The reason for this variability in temporal lobe atrophy in DLB is unknown, although based on a very limited autopsy examination of four cases, Harvey et al. (84) suggested that temporal lobe atrophy on MRI may be a marker of concurrent AD pathology in DLB. However, although cross-sectional imaging may be helpful in some cases, it clearly is not diagnostic. It is yet to be determined whether accurate longitudinal assessment of regional volume change on MRI increases the accuracy of diagnosis, as may be the case for AD (92).

In summary, the limited evidence available suggests that structural imaging in DLB reveals generalized atrophic changes similar to those of AD in most cases, although approximately 40% of DLB subjects show preservation of medial temporal lobe structures.

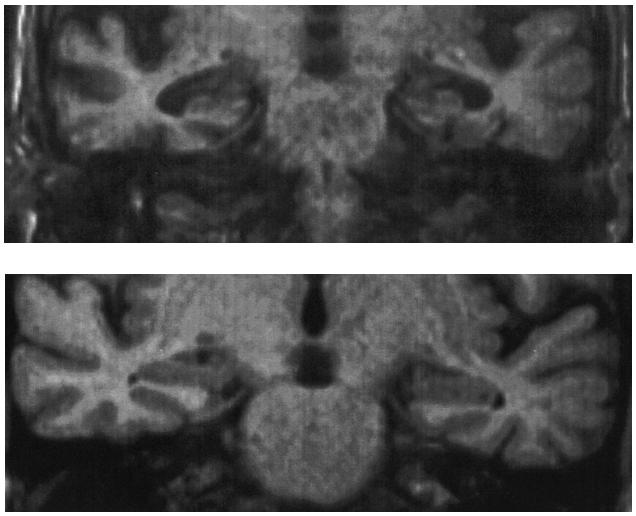

FIGURE 91.2. Coronal magnetic resonance imaging slices of patients with Alzheimer disease (AD) and dementia with Lewy bodies (DLB). Note severe atrophy of hippocampus and medial temporal lobe structures bilaterally in subject with AD. In contrast, the appearance of the medial temporal lobe in the subject with DLB is normal for age.

Functional Imaging Changes

Single-photon emission tomography (SPET) with the use of blood flow markers such as Tc-HMPAO (hexamethylpropylene amine oxime) has been extensively investigated in dementia. In AD, the classic appearance is one of posterior bilateral symmetric temporoparietal hypoperfusion (87,93), which contrasts with the frontal hypoperfusion characteristically seen in frontal lobe dementia (94). Vascular dementia is associated with a mottled, uneven, patchy appearance, reflecting the variable anatomic localization of vascular disease (95). In PD, the blood flow in basal ganglia is decreased, and when PD is associated with dementia, bilateral parietal changes similar to those seen in AD are reported (96,97). In the few SPET studies of DLB, patterns of blood flow changes similar to those of AD have been found, although Donnemiller et al. (98) found a subtle difference in perfusion patterns, with a greater degree of occipital hypoperfusion in DLB than in AD, and Defebvre et al. (99) found decreased frontal perfusion in DLB. Perfusion of the medial temporal lobe may be less impaired in DLB than in AD (100), consistent with the structural imaging findings described above of preservation of the same structures in DLB. Higuchi et al. (101) have suggested that glucose hypometabolism in occipital cortex is a diagnostic aid in distinguishing DLB from AD, and Imamura et al. (102) found that hypometabolism in this region in conjunction with relatively mild hypometabolism in temporal and parietal cortex is associated with visual hallucinations in DLB.

The more powerful, although still research-based, use of SPET involves the use of specific ligands for different neurochemical systems. Ligands have been developed for presynaptic and postsynaptic dopaminergic and cholinergic systems. Donnemiller et al. (98), using positron emission tomography (PET), found significant differences between DLB and AD in β-carbomethoxy-iodophenyl-tropane (CIT) binding (a ligand for the dopamine transporter), a difference that would be predicted from the known neurochemical differences between AD and DLB. However, one disadvantage of CIT is that imaging has to be delayed for 24 hours after injection. A single case report has suggested that a ligand with faster imaging kinetics, FP (fluoropropyl)-CIT, can distinguish DLB from AD (103). A reduced density of dopamine D2 receptors in basal ganglia, demonstrated with [^{123}I]iodobenzamide, has been reported in DLB (104). With use of a marker of the vesicular acetylcholine

transporter, significant differences between AD subjects and controls and between PD subjects with and without dementia have been found (105). In summary, current evidence suggests that SPET studies of blood flow show similar appearances in DLB and AD, although SPET may still be useful in distinguishing DLB, like AD, from frontal lobe dementia or vascular dementia. New chemical imaging techniques, although not yet clinically available, show great promise in differentiating DLB from other disorders and are an exciting area of current research.

TREATMENT

Neuropsychiatric Symptoms

Some of the key clinical features of DLB are similar to those induced in normal subjects by anticholinergic, specifically antimuscarinic, agents. Clouding of consciousness, confusion, and visual hallucinations are recognized effects of anticholinergic drug toxicity, and cumulative effects of subcortical and cortical cholinergic dysfunction probably play a major role in the spontaneous generation of similar fluctuating symptoms in DLB. As discussed in the earlier section on neurochemical clinical–pathologic relationships, reductions in choline acetyltransferase are correlated with cognitive impairment (75), and hallucinations may be related to hypocholinergic and (relatively) hypermonoaminergic neocortical neurotransmitter function (80).

Several reports have indicated that patients who respond well to cholinesterase inhibitor treatments are more likely to have DLB than AD at autopsy (106,107). This finding is consistent with the neurochemical profile of DLB and the fact that postsynaptic cortical muscarinic receptors are functionally intact. Case reports suggest that cholinesterase inhibitors can reduce psychotic symptoms in DLB (108), and a recently completed placebo-controlled study of rivastigmine in patients meeting consensus criteria for probable DLB found significant improvements in both neuropsychiatric features and cognition (109).

It is possible that cholinergic drugs may emerge as the antipsychotic treatment of choice in dementing diseases of the elderly, such as DLB. Not only are typical neuroleptics inappropriate (23); according to more recent reports, so are atypical drugs such as olanzapine (110,111).

Neurologic Symptoms

Because of the combination of parkinsonism with neuropsychiatric symptoms, the management of extrapyramidal signs in DLB is rather like walking a tightrope. The best outcome will invariably be a compromise between a relatively mobile but psychotic patient and a nonpsychotic but immobile patient.

Many currently available antiparkinsonian drug treatments, including monoamine oxidase B inhibitors, anticholinergic agents, and dopamine agonists, have an unacceptably high risk of precipitating or exacerbating hallucinations and confusion. In addition, most of these agents can cause or worsen orthostatic hypotension and lead to an increased incidence of falls. Although it has never been formally assessed, avoidance of these drugs in DLB patients would seem prudent. Indeed, for a DLB patient presenting with parkinsonism, in whom dementia and neuropsychiatric symptoms then develop, the first therapeutic decision should be to review the antiparkinsonian medication and undertake a gradual withdrawal if necessary.

At a practical level, the antiparkinsonian drug with the best risk-to-benefit ratio currently available for the treatment of extrapyramidal signs in DLB is levodopa. However, although the efficacy of levodopa for the treatment of PD is beyond question, how effective is this drug in the management of DLB? The evidence regarding the responsiveness of DLB patients to levodopa is conflicting. Some reports suggest that up to 100% of patients with DLB may improve, but the numbers of patients have usually been small in these series, and the degree of functional change and duration of the response have not been specified (39,40). Furthermore, the effects of levodopa therapy on neuropsychiatric symptoms are poorly documented in this group. Given the postsynaptic changes in dopamine D2 receptors noted in postmortem studies, it might be postulated that levodopa responsiveness is diminished in DLB. Clearly, a number of issues regarding the efficacy of dopaminergic treatment in DLB have not been resolved, and further trials are in progress to address these issues.

The most important point in the management of patients with DLB is to exercise caution in (or preferably avoid) prescribing neuroleptic medications, which are the mainstay of antipsychotic treatment in other groups of patients. Severe neuroleptic sensitivity reactions can precipitate irreversible parkinsonism, further impair the level of consciousness, and induce autonomic disturbances reminiscent of neuroleptic malignant syndrome (22,23). They occur in 40% to 50% of DLB patients treated with neuroleptics and are associated with a twofold to threefold increase in mortality. Acute blockade of D2 receptors is thought to mediate these effects, and despite some promising initial reports, atypical and novel antipsychotics such as risperidone and olanzapine seem to be just as likely to cause neuroleptic sensitivity reactions as the older drugs.

Until safe and effective medications become available, the mainstay of clinical management is undoubtedly to educate patients and carers about the nature of their symptoms and suggest strategies to cope with them. The clinician must ascertain which symptoms are most troublesome for the patient and explain the risks and benefits associated with changes in medication (112).

SUMMARY AND CONCLUSION

Dementia with Lewy bodies appears to be distinct both clinically and neuropathologically from AD and is the second most common form of degenerative dementia, accounting for up to 20% of cases in the elderly. It is characterized by fluctuating cognitive impairment, spontaneous parkinsonism, and recurrent visual hallucinations. Consensus clinical and neuropathologic criteria were published in 1996, and the clinical criteria have been shown to be highly specific, although they may still lack sensitivity. As in PD, the defining neuropathologic feature is the presence of Lewy bodies and neurites (positive for α-synuclein and ubiquitin) in a range of subcortical nuclei and in cortical regions, particularly cingulate and entorhinal. Alzheimer-type pathology is variable, ranging from none in the neocortex to, most commonly, extensive β-amyloidosis and, rarely, additional neurofibrillary tangle formation. The main neurotransmitter abnormalities include the following: extensive reduction in presynaptic cholinergic activities in the cortex, related to psychotic features such as hallucinations; elevations of muscarinic receptors; abnormalities in nicotinic receptors, related to disturbances in consciousness; and both presynaptic and postsynaptic dopamine abnormalities, related to extrapyramidal dysfunction, including sensitivity to neuroleptic medication. The recognition of DLB is clinically important in view of the high incidence (60%) of adverse and life-threatening reaction to antipsychotic medications, the difference in prognosis, and the differential treatment response to cholinergic therapy. Neuroimaging changes have not been described in DLB to any extent, but some show promise as potential markers to differentiate DLB from AD. These include relative preservation of temporal lobe structures on MRI and loss of presynaptic and postsynaptic dopaminergic markers on SPET. Patients with DLB respond positively to cholinesterase inhibitors with reductions in neuropsychiatric symptoms such as hallucinations, delusions, and agitation.

This chapter has summarized the major advances that have taken place within the last decade in understanding the mechanisms underlying DLB, in diagnosing the disease, and in treating some of the clinical features. In relation to neuropsychopharmacology, the disease provides a unique opportunity to understand mechanisms underlying symptoms such as hallucinations and disturbances in consciousness because such symptoms can occur in the absence of significant Alzheimer pathology and be correlated with quantifiable neurotransmitter abnormalities.

In terms of understanding the core pathologic mechanisms, however, as in AD and PD, the objective of disease prevention still appears to be a long way off. Transgenic mice expressing wild-type α-synuclein have synuclein-positive inclusions in cortex and substantia nigra and decreased dopamine levels in basal ganglia (113). It is interesting that this model, relevant to PD and DLB, expresses the phenotype in relation to transmitter abnormality (at least in regard to dopamine), whereas the equivalent model considered relevant to AD—overexpression of mutated amyloid precursor protein (APP)—does not. However, one report of numerous and widespread α-synuclein-negative Lewy bodies in an asymptomatic patient raises the question of just how pathogenic abnormalities of this synaptic protein really are (114).

With improved methods of diagnosing DLB now available, epidemiologic studies are needed. It would be interesting to determine whether tobacco use is associated with a decreased risk for the development of DLB, as it is for PD. The potential for neuroprotection based on stimulation of nicotinic receptors is increasingly being recognized (115).

Better genotype–phenotype correlation is also needed for DLB. For example, do functional polymorphisms within the dopamine D2-receptor gene influence levodopa responsiveness? In addition, does butyrylcholinesterase K homozygote status predict therapeutic response to cholinesterase inhibitors? Improved knowledge in this area could conceivably rationalize the use of drug treatments for DLB.

The involvement of brainstem nuclei in DLB other than the substantia nigra needs to be explored further. The quality of future clinicopathologic correlations will be enhanced by the prospective acquisition of clinical data in longitudinal studies with the use of standardized and validated instruments.

The role of levodopa in the treatment of the extrapyramidal syndrome associated with DLB needs to be defined better. For example, levodopa-induced ''on/off'' responses and dyskinesias have not been reported in DLB, as they have in PD. This may be because parkinsonism is generally less severe and may take longer to develop than DLB or because distinct striatal pathology (e.g., loss of cholinergic activity) is present. Novel therapies aimed at relieving parkinsonism that do not exacerbate neuropsychiatric features are needed. Drugs acting via nondopaminergic neurotransmitter systems may be applicable in this area (e.g., adenosine A_{2A} antagonists).

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