INTRODUCTION

Dementia with Lewy bodies (DLB) is a dementia syndrome associated with visual hallucinations, parkinsonism, and fluctuating levels of attention. “Necroepidemiological” studies place DLB second to Alzheimer’s disease (AD) in prevalence, accounting for 15–20% of all autopsy-confirmed dementias. The prevalence of clinically diagnosed DLB in a Finnish population aged 75 yr or older was found to be 5%, comprising 22% of all demented subjects. The association of Lewy bodies with Parkinson’s disease (PD) was made in 1912, but it was not until nearly 50 yr later, in 1961, that Okazaki and colleagues reported the association of the same inclusion body with severe dementia in two elderly male patients. In contrast to their brainstem counterparts, cortical Lewy bodies are less eosinophilic and lack a clear halo, making them more difficult to recognize using older haematoxylin and eosin staining methods. With the advent of more sensitive immunohistochemical techniques, notably ubiquitin and α-synuclein antibodies, a significantly greater burden of cortical Lewy body and neuritic pathology may be identified.

Cortical Lewy bodies may also be found in the majority of PD cases, with or without dementia, as well as in DLB. Alzheimer’s-type pathological features, notably senile plaques, frequently coexist in both DLB and PD with dementia (PDD). This “dual pathology” and clinicopathological overlap between PDD and DLB on the one hand and AD and DLB on the other, encapsulates the nosological debate currently surrounding DLB. Indeed, some authorities refer to DLB as the “Lewy body variant of Alzheimer’s disease,” although “dementia with Lewy bodies” is the preferred term, following a Consensus meeting in 1996.

This chapter will discuss the various components of the DLB clinical syndrome and explore the diagnostic issues that arise in differentiating DLB from PDD and AD. For details on the pathology the reader should see Chapters 4 and 8, and for the genetic aspects, Chapter 6.

CLINICAL FEATURES OF DEMENTIA WITH LEWY BODIES

The central feature of DLB is a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function, whereas core clinical components comprise fluctuating cognition, recurrent and persistent visual hallucinations, and extrapyramidal signs (EPS). Supportive features may increase diagnostic sensitivity, though exclusion criteria also need to be considered. Depression and REM sleep behavior disorder (RBD) have been suggested as additions to the list of supportive features.
A meta-analysis of 21 controlled comparisons has shown a clear and profound pattern of visual-perceptual and attentional-executive impairments in DLB (5). In terms of group differences, patients with DLB always do worse than age-matched controls on neuropsychological tasks, with particularly poor performance on visual perceptual and learning tasks, visual semantic tasks, and praxis tasks. Simple global measures of performance (e.g., the Mini Mental State Examination [MMSE]) are usually equivalent to those of patients with AD of comparable severity, highlighting the insensitivity of these tests to executive dysfunction. There are trends for better performance in DLB than AD patients on verbal memory and orientation tasks, for example, logical memory from the Wechsler Memory Scale. Patients with DLB lack the poor retention over delay intervals and increased propensity to produce intrusion errors in the cued recall condition, typical of AD. Performance on visual tasks, particularly praxis tasks, for example, Block Design from the Wechsler Adult Intelligence Scale, is consistently more impaired in DLB than in AD. A DLB patient will perform more poorly on simple bedside constructional tasks, for example copying a clock face, than an AD patient of comparable MMSE (6).

The neuropsychological changes with progression of DLB are not well characterized, though the clinical impression is that differences with AD are particularly pronounced in the early stages and, as the disease evolves, these lessen. Rate of progression, as evidenced by change in mental test scores, is equivalent to that seen in AD and vascular dementia (7).

Fluctuating Cognition

Variation in cognitive performance is commonly observed in all the major late-onset dementias. It is frustrating to carers and has a major impact upon the patient’s ability to reliably perform everyday activities. Fluctuating cognition (FC) may present in several ways, previously described as

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Table 1

Consensus Criteria for Clinical Diagnosis of Probable and Possible DLB

1. The central feature required for a diagnosis of DLB is progressive cognitive decline of sufficient magnitude to interfere with normal social and occupational function. Prominent or persistent 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 and one is essential for possible DLB:
   a. fluctuation of cognition with pronounced variations in attention and alertness
   b. recurrent visual hallucinations that are typically well formed and detailed
   c. spontaneous motor features of parkinsonism

3. Features supportive of the diagnosis are:
   a. repeated falls
   b. syncope
   c. transient loss of consciousness
   d. neuroleptic sensitivity
   e. systematized delusions
   f. hallucinations in other modalities
   g. REM sleep behavior disorder (4)
   h. depression (4)

4. A diagnosis of DLB is less likely in the presence of:
   a. stroke disease, evident as focal neurological 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

Adapted from ref. 3.
“sundowning” or “intermittent delirium,” depending upon the severity and diurnal pattern. FC occurs in 80% or more of DLB patients. The profile of attentional impairment and fluctuating attention in DLB is indistinguishable from that recorded in PDD (8).

The severity of FC can be judged by experienced clinicians and is highly correlated with variability in performance on computer-based attentional tasks. The variation can be detected over very short periods of time (on a second-to-second basis), suggesting that FC derives from dysfunction of continuously active arousal systems (9). Questions posed to the carer such as “are there times when his or her thinking seems quite clear and then becomes muddled” may be useful probes for this symptom. Substantial variability in attentiveness may also be observed throughout the consultation, or between one appointment and the next. The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale are validated instruments to record FC, correlating with both neuropsychological and electrophysiological measures of fluctuation (10).

Neuropsychiatric Features

A majority of DLB patients (80%) experience neuropsychiatric symptoms, particularly hallucinations, delusions, apathy, anxiety, and depression, at some stage of their illness (11). These symptoms may be quantified using the Neuropsychiatric Inventory (NPI), a 12-item interview with the caregiver rating frequency, severity, and associated carer distress of delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, aberrant motor behavior, sleep, and appetite disturbances (12). The NPI-4, comprising delusions, hallucinations, depression, and apathy, may represent a sufficiently sensitive abbreviated form of the NPI for practical use in the busy clinic setting for patient assessment (13).

Visual hallucinations (VHs) are a core feature in the Consensus Criteria for the clinical diagnosis of DLB. They are present in 33% of patients at the time of presentation (range 11–64%) and occur at some point in the course of the illness in 46% (13–80%) (14). VHs are the most common form of hallucination in DLB, although tactile, olfactory, and auditory hallucinations may also occur. The VHs are complex in type, often containing detailed scenes featuring mute people and animals (15). Affective responses to the hallucinations vary from indifference, to amusement, or fear and combativeness. VHs and delusions often coexist, common delusions being phantom border delusions (i.e., the belief that strangers live in the home), or paranoid delusions of persecution, theft, and spousal infidelity. Delusions and hallucinations often trigger other behavioral problems, such as aggression and agitation, leading to profound caregiver distress and precipitating early nursing home admission.

VHs in DLB correlate strongly with Lewy body density in parahippocampal and inferior temporal lobe cortices (16). See also Chapter 11.

Extrapyramidal Signs

The frequency of parkinsonian features at presentation in DLB ranges between 10% and 78%, with 40–100% of DLB cases displaying EPS at some stage of the illness (17–19), with differences likely to represent ascertainment bias, use of neuroleptic agents, and variable definition of clinical phenomenology.

The Phenomenology of the Extrapyramidal Syndrome in DLB

Louis and coworkers compared EPS in 31 DLB and 34 PD pathologically confirmed cases (17). Clinical information was obtained prospectively in some patients. DLB patients presenting with parkinsonism were, on average, 10 yr younger than the DLB patients presenting with neuropsychiatric features (60.0 vs 70.9 yr). Of the DLB patients, 92% had at least one sign of parkinsonism, with 92% having either rigidity or bradykinesia. A tremor of any type or a specific rest tremor was recorded in 76% and 55%, respectively, of the DLB patients. This compared with 88% and 85%, respectively, of the PD group. Myoclonus was documented in 18.5% of the DLB patients but none of the PD group.
A trial of levodopa was used in 42% of the DLB group, with a clinical response recorded in 7 of the 10 patients (70%). The dose of levodopa required and the precise nature of the response were not stated. In attempting to differentiate DLB from PD on the basis of the Parkinsonian syndrome, the authors concluded that patients with DLB were 10 times more likely to have one of four clinical features (myoclonus, absence of rest tremor, no perceived need to treat with levodopa, and no response to levodopa). The positive predictive value for having DLB, given any one of these features was 85.7% (sensitivity 66.7%, specificity 85.7%).

Gnanalingham and colleagues reported a comparison of clinical features, including EPS, in 16 DLB, 15 PD, and 25 AD patients, diagnosed according to published clinical criteria (20). Nine of 16 DLB patients (56%) presented with EPS and 15 (94%) qualified for a "second diagnosis" of PD. A greater rigidity score, assessed using the Unified Parkinson’s Disease Rating Scale (UPDRS), and lower scores on a finger-tapping test were more frequently noted in the DLB patients compared with the PD group, whereas resting tremor and left/right asymmetry were less common. Twelve of 16 (75%) DLB patients had received levodopa at some stage of their disease, and 10 were taking anti-parkinsonian drugs at the time of the study. All cases were noted to have treatment "responsiveness," although the degree of motor improvement and the doses required were not stated.

An international, multicenter study reported parkinsonism in 92.4% of 120 DLB patients (19). There was a small but statistically significant difference between male and female patients on a five-item UPDRS subscale (the UPDRS-5), with male DLB patients more severely affected. This modified subscale comprising rest tremor, action tremor, bradykinesia, facial expression, and rigidity, is independent of the severity of cognitive impairment (21). Older DLB patients tended to have higher UPDRS scores, but the difference was not statistically significant. Cases with severe cognitive impairment (MMSE < 18) had significantly more severe EPS than those with less cognitive decline using the full UPDRS part III, but when this relationship was reexamined using the UPDRS-5 there was no difference between the groups. Patients with more severe dementia may thus have difficulty understanding and executing some of the instructions. It is thus likely that severity of parkinsonism is independent of cognitive decline.

Aarsland and colleagues compared EPS in 98 DLB and 130 PD patients (18). The DLB group was older at time of assessment and had a shorter duration of disease compared with the PD patients. Sixty-seven of the DLB patients (68%) had EPS. More severe action tremor, rigidity, bradykinesia, difficulty arising from a chair, greater facial impassivity, and gait disturbance were described in the DLB group.

The Spectrum of Parkinsonism in PD With and Without Dementia and DLB

Does the parkinsonian syndrome associated with DLB differ fundamentally from that seen in PD? This seems highly improbable, and though clinical series may describe higher or lower frequencies of certain EPS in DLB compared with PD, there are no absolute discriminating features. The pattern of EPS in DLB does, however, seem to show an axial bias (e.g., greater postural instability and facial impassivity), with a tendency toward less tremor, consistent with greater “non-dopaminergic” motor involvement. According to the classification proposed by Jankovic based upon the UPDRS II and III (22), the postural instability-gait difficulty (PIGD) phenotype of parkinsonism is overrepresented in DLB, as indeed it may be in PDD (23). EPS in PD, PDD, and DLB may thus be a spectrum, with a shift toward greater non-dopaminergic motor system involvement through PD to DLB. This is consistent with previous studies reporting motor features mediated by non-dopaminergic pathways (speech, posture, and balance) correlating with incident dementia in PD (24).

Progression of Parkinsonism in DLB

DLB patients with established parkinsonism have an annual increase in severity, assessed using the UPDRS, of 9%, a figure comparable with PD (25). In contrast, and again in common with PD, progression is more rapid in DLB patients with early parkinsonism (49% increase in motor UPDRS score in 1 yr).
Falls, Syncope, Sleep Disorders, and Other Neurological Features

A retrospective clinical analysis of pathologically confirmed cases of PD and DLB revealed that falls occurred at some point in the disease duration in 91% of 11 and 79% of 14 cases, respectively (26). The mean latency to onset of recurrent falls was, however, much shorter in the DLB group at 48 months, compared with 118 mo in the PD group. In a prospective study, multiple falls (defined as more than five falls) occurred in 37% of 30 DLB patients and only 6% of 35 AD patients (27). The falls often resulted in injury. Other than having DLB, multiple falls were associated with parkinsonism, previous falls, greater impairment of activities of daily living, and older age.

Several pathophysiological mechanisms could underlie the falls in DLB, including degeneration of brainstem nuclei, for example, the pedunculopontine nucleus, and impaired visuospatial processing. Orthostatic hypotension, vasovagal syncope, and carotid sinus hypersensitivity, collectively referred to as neurovascular instability, are common in patients with neurodegenerative dementia, and also contribute to falls. Cardioinhibitory carotid sinus hypersensitivity may reflect monoaminergic neuronal loss within cerebrovascular brainstem centers (28).

A supranuclear gaze paresis has been described in DLB (29–31). In combination with cognitive impairment and falls, this may cause diagnostic confusion with Steele–Richardson–Olszewski syndrome (progressive supranuclear palsy [PSP]). Other neurological features rarely described in DLB include an alien limb (32), chorea and dystonia (33).

Sleep disturbance is more common in DLB than in AD, as are daytime drowsiness and confusion on waking (34). RBD is characteristic of synucleinopathic disorders and frequently commences before the onset of dementia in DLB, sometimes by up to 20 yr (35). Over 90% of patients with RBD and degenerative dementia meet criteria for possible or probable DLB (36).

DIAGNOSTIC ACCURACY AND DIFFERENTIAL DIAGNOSIS

Five sets of diagnostic criteria have been proposed to date to assist in the accurate diagnosis of DLB (37). The most rigorous approach led to the formulation of the Consensus criteria (Table 1) (3). Considering all the published studies together that have reported the diagnostic accuracy of the Consensus criteria yields a mean sensitivity of 49% (range 0–83%) and specificity of 92% (79–100%) (37). All these studies compared DLB to other dementia syndromes, including AD or vascular dementia, and the majority was retrospective. Discriminating value for the Consensus criteria is greatest at an early stage, suggesting that DLB should be considered in any new dementia presentation (38).

Interrater reliability for the core clinical features of parkinsonism and hallucinations in DLB is generally good, but only poor or moderate for fluctuating cognition. The application of validated methods to recognize the latter may thus increase diagnostic accuracy.

Perhaps unsurprisingly, AD is the most frequent misdiagnosis in autopsy-confirmed DLB cases (39,40). Pathologically, of course, the situation is frequently not clear-cut, with a variable admixture of plaques and tangles, in addition to synuclein-positive inclusions. The degree of concomitant AD tangle pathology has an important influence upon both the clinical diagnostic accuracy of DLB and the clinical phenotype. In one study, the clinical diagnostic accuracy for DLB cases with low Braak staging was 75% compared to only 39% in those cases with high Braak stages (41). High-Braak stage DLB cases are also less likely to experience VHs during the disease course.

Despite a significant overlap in neuropathological and clinical features with DLB, Consensus guidelines suggest that PD patients developing dementia more than 12 mo after the initial motor symptoms should be diagnosed as PDD rather than DLB. At least 25–30% of PD patients are demented in cross-sectional studies (18) although the cumulative incidence of dementia is nearer 80% (42). Future research needs to clarify whether PDD and DLB are different representations of the same neuropathological process, with different early clinical manifestations, or whether they are independent disease processes ending in a similar common pathway.
When DLB presents as a primary dementia syndrome the key differential diagnoses are AD, vascular dementia, delirium secondary to systemic or pharmacological toxicity, Creutzfeldt-Jakob disease, or other neurodegenerative syndromes characterized by EPS and dementia. The latter include PSP and corticobasal degeneration (CBD). These conditions need to be excluded as far as possible by taking a careful history (including the carer whenever possible) and performing a thorough neurological examination, supplemented where necessary by ancillary investigations (see next section, Investigation). Table 2 summarizes the key clinical features in several neurodegenerative syndromes featuring parkinsonism and cognitive impairment.

The value of simple bedside tests of cognitive function should not be overlooked. For example, the inability of moderately impaired DLB patients to accurately copy pentagons has been reported with a sensitivity of 88% and specificity of 59% compared with AD (6).

INVESTIGATION

No specific serum or cerebrospinal fluid biomarkers are yet available to increase diagnostic accuracy for DLB. Genetic testing cannot be recommended at present as part of the routine diagnostic process. Most DLB cases are sporadic, although there are a few reports of autosomal dominant Lewy body disease families (43,44). The APOE4 allele is overrepresented in DLB as in AD but not in PD without dementia (45). No robust associations have been found between polymorphisms linked with familial AD and DLB. The APP717 mutation, however, may be associated with familial AD and extensive cortical Lewy bodies (46).

The additional value of ancillary investigations in the diagnostic process for DLB is also uncertain, although the development and validation of functional neuroimaging techniques, in particular, will almost certainly improve upon current clinical diagnostic sensitivity.

Neuroimaging

Structural Imaging Changes in DLB

Relative preservation of the hippocampal and medial temporal lobe compared to AD is characteristic of DLB (47), possibly helping to explain the preservation of mnemonic function. Although hippocampal volume is reduced, by around 15% compared to controls, the reduction is considerably less than that seen in AD, with some 40% of DLB cases having no evidence of any atrophy. Rate of volume loss over time using serial magnetic resonance imaging (MRI) is comparable with AD (2% per year in AD and DLB compared with 0.5% in controls) (48). There are increased white matter lesions in AD and these may contribute to the cognitive impairment. A similar increase has been described in DLB cases (49), though effects on cognitive function have not yet been determined.

Functional Imaging Changes in DLB

Fluorodeoxyglucose positron emission tomography (PET) and single photon computed tomography (SPECT) studies using blood flow markers such as 99mTc-HMPAO demonstrate many similarities between DLB and AD subjects (50,51), with pronounced biparietal hypoperfusion and variable, usually symmetric, deficits in frontal and temporal lobes. The biparietal hypoperfusion in DLB is, however, more extensive than in AD cases matched for age and dementia severity, particularly in Brodmann area 7, an area subserving visuospatial function (52).

Occipital hypometabolism on PET and SPECT is characteristic of DLB and affects both primary visual cortex as well as visual association areas (Brodmann areas 17–19). Occipital hypoperfusion has reasonable specificity (86%) for distinguishing DLB from AD and controls, although the sensitivity for this finding is relatively low (64%) (51). Consistent with findings from structural imaging studies, temporal lobe perfusion is relatively preserved in DLB.

Significant reductions in striatal binding of β-carbomethoxy-iodophenyl-tropane (a ligand for the dopamine transporter) using PET have been demonstrated in DLB but not AD, a difference that
Table 2  
Comparison of Neurodegenerative Diseases Featuring Parkinsonism and Cognitive Impairment

<table>
<thead>
<tr>
<th></th>
<th>DLB</th>
<th>PD</th>
<th>AD</th>
<th>PSP</th>
<th>CBD</th>
<th>MSA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parkinsonism</strong></td>
<td>symmetric, PIGD</td>
<td>asymmetric, TD, and late PIGD</td>
<td>variable, usually mild, late</td>
<td>symmetric bradykinesia ++, PIGD</td>
<td>marked asymmetry, rigidity dominant</td>
<td>symmetric bradykinesia, PIGD (often early)</td>
</tr>
<tr>
<td>* L-dopa response</td>
<td>++</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–/++ (waning)</td>
</tr>
<tr>
<td><strong>Other motor features</strong></td>
<td>myoclonus</td>
<td>Gegenhalten (paratonia)</td>
<td>alien limb, stimulus-sensitive myoclonus, dystonia, ideomotor apraxia</td>
<td>cerbellar ataxia, myoclonus</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Eye movements</strong></td>
<td>impaired saccade triggering</td>
<td>normal</td>
<td>normal</td>
<td>SNGP/slow vertical saccades</td>
<td>increased saccadic latency (speed N)</td>
<td>mild saccadic slowing</td>
</tr>
<tr>
<td><strong>Autonomic failure</strong></td>
<td>++ (may be early)</td>
<td>++ (often late)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+++ (often early)</td>
</tr>
<tr>
<td><strong>Dementia</strong></td>
<td>early, executive, and visuospatial</td>
<td>early, severe memory deficit</td>
<td>fronto-subcortical and apathy</td>
<td>frontal dementia may be early feature</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neuropsychiatric features</strong></td>
<td>* VH</td>
<td>+++</td>
<td>++ (usually late)</td>
<td>*</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>* depression</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+ (apathy)</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

*, absent; + to +++ frequency of feature; N, normal; SNGP, supranuclear gaze palsy; PIGD, postural instability–gait difficulty; TD, tremor dominant; VH, visual hallucination.
would be predicted from the nigrostriatal dopaminergic pathology associated with DLB (53). FP-CIT SPECT can also differentiate DLB from AD (54). Scintigraphy with [123I]metaiodobenzyl guanidine (MIBG) enables quantification of postganglionic sympathetic cardiac innervation. Cardiac MIBG scanning can differentiate DLB (where the signal is reduced) from AD (where the signal is similar to control values) (55,56).

Neurophysiological Studies

The electroencephalogram (EEG) is diffusely abnormal in over 90% of DLB patients. Early slowing of the dominant rhythm, with 4- to 7-Hz transient activity over the temporal lobe area, is characteristic and correlates with a clinical history of loss of consciousness (57). It is not possible to reliably differentiate DLB and AD subjects on the basis of the EEG, however (58). The diagnostic significance of bursts of bilateral frontal rhythmic delta activity, reported to be more common in DLB than AD, has yet to be established (59). Multifocal action myoclonus, which occurs in approx 15% of DLB patients, is clinically more severe than that associated with PD, although it has the same electrophysiological characteristics. The balance of evidence favors a cortical source for the myoclonus (60). Since myoclonus also occurs in AD, it will be interesting to determine whether concomitant cortical Alzheimer’s-type pathology influences the presence and severity of the myoclonus in Lewy body disorders.

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DLB patients have fewer and abnormally delayed auditory startle responses (ASRs) of low amplitude and short duration in extremity muscles compared with healthy controls (61). Virtually no responses may be elicited in the lower limbs. Interestingly, the reduced ASR probability in advanced DLB is similar to that found in PD patients with postural instability and recurrent falls, suggesting a common brainstem pathophysiological mechanism for both disorders.

MANAGEMENT

General Considerations

Nonpharmacologic strategies for cognitive symptoms in DLB include orientation and memory prompts and attentional cues, although such approaches are of limited benefit. For psychiatric symptoms, explanation, education, reassurance, and targeted behavioral interventions may alleviate patient and carer distress.

In the acutely confused and psychotic patient, intercurrent infection and subdural haematoma should be excluded. Other nonessential medication capable of causing confusion should be discontinued. Potential therapeutic conflict may arise in the management of DLB over the so-called “motion-emotion” conundrum, whereby measures to alleviate psychosis and cognitive deficits may lead to deterioration in motor function and vice versa. Anti-parkinsonian drug treatment, if necessary, should be restricted to levodopa. Anticholinergics, amantadine, selegiline, and dopamine agonists should generally be avoided (14) (Fig. 1).

Nearly 50% of DLB patients receiving conventional high-affinity dopamine D2 receptor antipsychotic agents experience life-threatening adverse effects, termed neuroleptic sensitivity reactions, characterized by sedation, rigidity, postural instability, falls, and increased confusion, and associated with a two- to threefold increased mortality (62). Even the use of so-called “atypical” antipsychotic drugs may be associated with neuroleptic sensitivity reactions and low dosing may be more important than the use of any specific drug (63–65).

Cholinesterase Inhibitors in DLB

There is converging and consistent evidence that cholinesterase inhibitors (ChEIs) are effective and relatively safe in the treatment of neuropsychiatric and cognitive symptoms in DLB. Open studies of donepezil and rivastigmine have reported improvement in cognitive and noncognitive symptoms, without significant deterioration in motor function (66,67). A placebo-controlled, double-blind
study assessed the effect of rivastigmine (mean dose 7mg/d) in 120 DLB patients over 20 wk, followed by a 3-wk withdrawal period (68). Patients taking rivastigmine were less apathetic, less anxious, and had fewer delusions and hallucinations compared to placebo controls. Treatment effects disappeared on drug withdrawal.

The long-term efficacy of rivastigmine was further assessed in an open-label study over 96 wk (69). Improvements in cognitive and neuropsychiatric symptoms were noted after 24 wk, returning to pretreatment levels after 36 wk. The presence, rather than absence, of VHs in DLB may predict a good response to ChEIs, as evidenced by improved attention measures (70). In autopsy studies, DLB cases with VHs have lower levels of cortical choline acetyltransferase, particularly in temporoparietal regions, compared with DLB patients without VHs (71). This may allow greater clinical improvements to occur, with cholinergic replacement therapy having a more marked effect upon a lower neurochemical baseline.

ChEIs are well tolerated in DLB subjects, with dropout rates (10–31%) and gastrointestinal side effects similar to those found in AD. Hypersalivation, rhinorhea, and lacrimation may also occur in approx 15% of DLB and PDD patients treated with donepezil (72). An early report of worsening of parkinsonism in two of nine patients treated with donepezil has not been replicated in other studies, which have consistently demonstrated either no change or improvement in EPS during ChEI therapy (73).
Other Pharmacological Management of DLB

No placebo-controlled study has assessed the effects of antidepressant drugs in DLB. Tricyclic antidepressants (e.g., amitriptyline, clomipramine, nortriptyline) should be avoided because of their anticholinergic side effects and potential to exacerbate orthostatic hypotension. Selective serotonin reuptake inhibitors (e.g., citalopram, sertraline, paroxetine) and the multireceptor antidepressants (e.g., nefazodone, mirtazapine, and venlafaxine) may therefore be better options for the treatment of depressed DLB patients (74).

Sleep disturbances, particularly RBD, may be cautiously treated with low-dose clonazepam (0.25–1.0 mg) at bedtime (36). Anticonvulsant drugs (e.g., carbamazepine, sodium valproate) may be occasionally necessary to treat significant behavioral disturbances, although randomized controlled trial data are lacking (75).

CONCLUSION AND FUTURE DIRECTIONS

DLB is a relatively “young” disease, in which the clinicopathological overlap between PD and AD needs to be better defined. An accurate diagnosis of DLB has significant management and prognostic implications for the patient; an improved diagnostic awareness is therefore important. Information derived through the study of DLB may ultimately benefit patients with other synucleinopathies. For example, the successful use of ChEI drugs in DLB has encouraged the design of trials and use of these agents in PDD, strengthened by our knowledge of similar underlying pathophysiological mechanisms.

Table 3 lists a number of future research directions for DLB. These include a better understanding of underlying molecular biological mechanisms underpinning the disease, defining the role of additional investigations in refining diagnostic accuracy, and improved therapeutic approaches. Although clearly something of a “wish list,” studies are already under way to address several of these issues.
Dementia With Lewy Bodies

LEGEND TO VIDEOTAPE

This video shows a 67-yr-old patient with a two-year history of probable DLB (MMSE 21), with no previous neurological, psychiatric or medical history. Parkinsonian features appeared within the first year of cognitive impairment. Medication comprised a cholinesterase inhibitor and low dose co-careldopa.

Sequence 1: The caregiver’s view of early symptoms (including visuospatial problems and REM-sleep behaviour disorder)

Sequence 2: The patient’s description of his visual hallucinations, occurring usually at night, but not when falling asleep or waking up.

Sequence 3: Assessment of parkinsonian features, including reduced blink rate, significant hypomimia, monotonous speech, bradyphrenia, limb bradykinesia and reduced arm swing when walking.

Sequence 4: Illustrative components of the bedside cognitive assessment. Memory function is relatively preserved (learning of three words and recall), but there are difficulties in visuo-constructive function (slowing and errors on the clock face including clock hands having the same length, and use of a “0” instead of “9”).

REFERENCES


