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Dementia with Lewy bodies

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Synopsis

The advent of new immunostains have improved our ability to detect limbic and cortical Lewy bodies, and it is now evident that Dementa with Lewy bodies (DLB) is the second most common neurodegenerative dementia, after Alzheimer's disease (AD). Distinguishing DLB from AD has important implications for treatment, in terms of substances that may worsen symptoms (i.e., anticholinergic and certain neuroleptic medications) and those that may improve them (i.e., cholinesterase inhibitors, carbidopa-levodopa). Neurocognitive patterns, psychiatric features, extrapyramidal signs and sleep disturbance are helpful in differentiating DLB from AD early in the disease course. Differences in the severity of cholinergic depletion as well as type and distribution of neuropathology contribute to these clinical differences, though DLB patients with a high density of co-occuring AD pathology are less clinical distinguishable from AD.

Keywords

Lewy bodies; dementia; parkinsonism; hallucinations; fluctuations

Introduction

Neocortical Lewy bodies are found in about 20–35% of elderly persons with dementia (1–4) and do not commonly occur in normal brains (5). Based on sensitive immunostaining techniques, dementia with Lewy bodies (DLB) is now considered the second most common cause of neurodegenerative dementia following Alzheimer's disease (AD)(5,6). In 1996, consensus criteria for the clinical diagnosis of DLB were put forth that require dementia plus one or two of the following core features (2 for probable DLB, 1 for possible DLB): Recurrent fully formed visual hallucinations (VH), parkinsonism and fluctuating cognition. (7) Using these criteria, diagnostic accuracy varies from poor to excellent(8–11). Problems with reliable assessment of fluctuations, a lack of empiric data regarding when core features should occur relative to dementia onset, and limitations to study design (e.g., circularity, absence of standardized assessment, inclusion of cases with advanced dementia) contribute to this discrepancy(12–16). The 3rd international workshop on DLB and Parkinson's disease dementia (PDD) convened in 2003 and revised consensus diagnostic criteria have been recently published (17). These criteria are presented in Table 1.

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Neuropsychological Function

The dementias of DLB and AD are similar in insidious onset and progressive course, and prior to autopsy, many patients with Lewy body disease are given the antemortem diagnosis of AD(3,13). Despite some similarities, several studies show greater deficits in attention and visual-perception in DLB, while AD is associated with worse memory and naming(3,18–20). Logistic regression modeling was done to determine the diagnostic utility of cognitive assessment in the differentiation of a prospective sample of persons with DLB (n=87) from those with AD (n=138) and normal aging (n=103)(21). Patient groups did not differ in age, education or dementia severity. The logistic models reveal that impairment in basic attention, visual perception, visual construction and memory distinguished DLB from normal aging (sensitivity of 88.6%, specificity of 96.1%). In contrast, impaired visual construction and attention plus preserved memory and naming skills distinguished DLB from AD (sensitivity of 83.3% and a specificity of 91.4%). These results confirm our prior findings of a double dissociation in neurocognitive function between early DLB and AD(21).

The higher order visual processing deficits in DLB is a finding that is not attributable to motor slowness associated with parkinsonism(3,20,22–26). The perceptual deficits evident in DLB may be responsible for some misperceptions (i.e., illusions) and delusional misidentification (i.e., not recognizing family, reduplicative paramnesia). Interestingly, DLB patients with visual hallucinations tend to do more poorly on visual tasks(19–25,27). Nonetheless, some studies have not found differences between AD and DLB on visual tasks(28,29), though this may be due to methodologic issues, such as the inclusion of patients in the advanced stages of dementia which can obfuscate group differences due to generalized impairment. Alternately, differential impairment of other task demands may be a factor. For example, visual problem solving may be negatively affected by executive difficulties in AD, and by perceptual difficulties in DLB. Mori and colleagues examined this issue and revealed deficits in DLB but not AD on basic visual tasks that do not require executive function(30). Also, a distinction between spatial and perceptual processing seems to be a distinguishing factor as well, with DLB patients showing greater deficits in the latter(31). There may be group differences in how the information is initially encoded. Reflexive saccadic eye movements responsible for repositioning the fovea show greater impairment for DLB compared to AD(32), and regional blood flow has been shown to be lower in occipital regions in DLB despite the relative absence of Lewy pathology there (33–36). Overall, visual processing deficits in DLB may be due to disruption of the cortical extra-striate association areas (especially the ventral visual pathway), but there may also be disruption to the afferent system (perhaps via mechanisms subserving saccadic foveation) before reaching the primary visual cortex.

Memory difficulties, when present in early DLB, appear to be fairly mild and stand in direct contrast to the pronounced amnestic disturbance of AD(18–20). Neuropathologic and imaging studies also show significant atrophy in the hippocampus in AD, while patients with DLB show little difference from normal controls(37–39). Salmon and colleagues(18) demonstrated a pattern of poor initial learning and retrieval in 4 of 5 patients with DLB without the rapid forgetting that is typically observed in AD. In a sample of 9 pure DLB, 57 mixed DLB/AD and 66 pure AD, patients with AD pathology performed worse on tasks of verbal memory while patients with LB pathology performed worse on tasks of visual spatial skills, and combined pathology affected visual spatial performance but not verbal memory(40).

Spontaneous Motor Features of Parkinsonism

For diagnostic clarity, parkinsonian signs must be spontaneous and not attributable to neuroleptics(7). Cognitive impairment in PD and DLB is more often associated with rigidity and bradykinesia than tremor(41–50). Postural instability/gait difficulty is over-represented in DLB and PDD compared to PD(51), and this has led some to speculate extrapyramidal signs associated with dementia may have a dopaminergic and non-dopaminergic basis. In general, the parkinsonism associated with DLB tends to be less severe than that observed in PD or PDD, at least initially. Tremor, bradykinesia and rigidity tend to be more symmetric than asymmetric, and tremor tends to be maximal with posture/action rather than at rest. One study of 14 DLB, 28 PD and 30 PDD patients showed improvement in Unified Parkinson's Disease Rating Scale (UPDRS) score for all 3 groups in response to l-dopa, but less so for the DLB patients(52). The possibility that this effect may be mediated by greater initial motor deficits in the PDD and PD groups should be considered.

Visual Hallucinations

Visual hallucinations (VH) in DLB consist of fully formed, detailed, three-dimensional objects, people or animals that are not attributable to perceptual distortion or illusion(3,47,53). DLB patients with auditory hallucinations (AH) typically experience VH, but AH rarely occur in patients without VH (54,55). Hallucinations in DLB do not occur as a function of AD pathology(56) and are not associated with levodopa dose or the presence of "on" (able to move) and "off" (unable to move) states(57). VH have been documented to occur in 59–85% of autopsy confirmed DLB samples, and in 11–28% of autopsy confirmed AD samples(5,15,58,59). Autopsy studies reveal that VH are most likely to occur early in DLB disease course while they tend to occur in the advanced stages of AD (5,60–62). In an autopsy study of 41 DLB and 70 AD, a cut-off of 4 years for the onset of hallucinations relative to dementia onset improved the positive and negative predictive values of DLB to 81% and 79%, respectively(63). Patients with VH typically have greater cognitive and functional impairment(64–68), but whether the presence of VH in DLB is associated with faster rate of disease progression has yet to be determined. The underlying cause of hallucinations is most likely associated with the severe depletion of acetylcholine in DLB, but other neurotransmitter systems may have a contributory role, including dopamine and serotonin. Involvement of the basal forebrain and the ventral temporal lobe have been implicated in the causation of visual hallucinations given their respective cholinergic and visual perceptual roles (5,58). Also, the dysregulation of rapid eye movement (REM) sleep in many patients with DLB, raises the possibility that the intrusion of dream imagery into wakefulness as a potential mechanism (69,70). These etiologies are not necessarily mutually exclusive.

Fluctuations

The fluctuations of DLB resemble signs of delirium without identifiable precipitants of such mental status changes. This phenomenon involves a waxing and waning of cognition, abilities and arousal. It has been described as variable attention, incoherent speech, hypersomnolence, impaired awareness of surroundings, staring into space, or appearing "glazed" or "switched off". The prevalence of fluctuations in DLB samples is widely discrepant and ranges from 10 to 80% with poor inter-rater reliability (8,10,12,71,72). Studies typically do not specify how the presence of fluctuations was determined and the usefulness of this core clinical feature has been highly criticized. Available techniques to assess fluctuations include a brief interview rating scale relying on clinical expertise, a semi-structured interview that inquires about the day before the assessment(16,73–76), and a set of 4 questions derived from a lengthier questionnaire (77). The latter questionnaire was

designed to determine whether there are salient features of fluctuations that reliably differentiate DLB (n=70) from AD (n=70) and normal elderly (n=200). Results show that four items significantly differentiated DLB from AD and include: 1. daytime drowsiness and lethargy, 2. daytime sleep of 2 or more hours, 3. staring into space for long periods and 4. times when the patient's flow of ideas seem disorganized, unclear or not logical. The presence of 3 or 4 features of this composite occurred in 63% of DLB compared to 12% of AD and 0.5% normal elderly ($p<0.01$). A score of 3 or 4 yields a positive predictive value of 83% for the clinical diagnosis of DLB against an alternate diagnosis of AD, and a score of less than 3 yields a negative predictive value of 70% for the absence of DLB in favor of AD. Since not all patients with DLB have fluctuations, these values suggest reasonable diagnostic utility. No particular combination of visual hallucinations, parkinsonism (presence or severity) or RBD was associated with a fluctuations composite score of 3 or 4. (77) These data indicate that an informant-based questionnaire is sensitive to fluctuations in alertness and speech, but fails to differentiate fluctuations in ability or cognition between DLB and AD. It may be worthwhile to distinguish between fluctuations in arousal and cognition, whereby the latter may be best evaluated with neuropsychometric tests. This is supported by findings that attention, vigilance and reaction time show greater impairment and variability in DLB than in AD (20,73,75).

Excessive daytime drowsiness

Patients with DLB often have daytime drowsiness or somnolence. As such, ruling out known causes of daytime sleepiness, including medications and primary sleep disorders (i.e., sleep apnea) is critical. In a clinical referral sample of 78 patients with early DLB who underwent overnight polysomnography, about 3/4 of the sample had a significant number of arousals not accounted for by medication, periodic limb movements of sleep or sleep apnea(78,79). In half of the DLB sample, sleep efficiency fell well below the expected 80% for this age group(80–82). This raises the possibility that dysfunction of brainstem and/or hypothalamic neuronal networks subserving sleep/wakefulness may be producing daytime drowsiness. Further studies are needed that represent a random selection of DLB patients and an AD group matched for age, gender and dementia severity.

REM Sleep Behavior Disorder (RBD)

The loss of normal muscle atonia during rapid eye movement (REM) sleep refers to the parasomnia of REM Sleep Behavior Disorder (RBD). In RBD, augmented muscle activity during REM sleep occurs along with altered dream content, and can range from elevated muscle tone to complex behavioral sequences such as pantomiming various activities that may be subdued or quite vigorous (22,83). The presumed pathophysiologic mechanism of RBD, involves damage to the descending pontine-medullary reticular formation (including the magnocellular reticular formation) and/or sublaterodorsal nucleus that leads to a loss of the normal REM sleep inhibition of the spinal alpha-motoneurons (84–87). In humans, polysomnographic evidence of REM sleep without atonia is considered the electrophysiologic substrate of RBD and has been found in patients with and without florid RBD (88,89). RBD can precede the onset of neurodegenerative diseases with alpha-synuclein inclusions (i.e., DLB, Parkinson's disease, Multiple System Atrophy) by years and even decades(22,89–94). It rarely occurs in tau-predominant neurodegenerative conditions, such as Alzheimer's disease (92). Neuropathologic confirmation of Lewy body disease has been demonstrated in a patient with a 20-year history of idiopathic RBD (93), and in a patient with a 15-year history of idiopathic RBD(94), neither of whom had any other neurologic signs or symptoms or evidence of psychosis. Out of 36 patients with clear clinical histories of RBD, 31 had Lewy body disease, 4 had Multiple System Atrophy and 1

has progressive supranuclear palsy, providing further evidence that RBD usually reflects an underlying synucleinopathy (95).

The estimated onset of RBD typically precedes the onset of dementia, visual hallucinations and parkinsonism by many years and often decades (range= 6 months to 55 years) (19,20,22). Despite this relationship, patients who initially present with dementia and RBD will not meet formal DLB criteria until parkinsonism or hallucinations become apparent. We examined the neurocognitive performance of 25 patients with RBD and dementia (without parkinsonism or hallucinations) and compared them to 37 patients with clinically probable DLB and 30 autopsy-confirmed AD of matched dementia severity (19). Results indicate that the DLB and RBD plus dementia groups were cognitively indistinguishable, but both groups significantly differed from autopsy-confirmed AD patients of matched dementia severity. Follow-up data from a subset of patients with RBD plus dementia revealed the subsequent development of parkinsonism and/or VH one to six years later. Thus, a clinical history of RBD in the context of dementia with disproportionate visual deficits and relatively preserved memory and naming is likely to represent the earliest stages of DLB.

Dysautonomia

Autonomic abnormalities, in particular orthostatic hypotension and carotid sinus sensitivity are more common in DLB than AD or elderly controls (17). A comparison of dysautonomia in DLB, PD and MSA shows that orthostatic hypotension is quite common in all 3 groups but MSA is the most severely affected, PD is least severely affected, and DLB has intermediate severity (96). The DLB group tended to respond better to medications than those with MSA. The frequency of urinary symptoms and pattern of sweat loss in DLB was comparable to that of PD but much less than MSA.

Rate of decline in DLB

Several studies of DLB indicate a more rapid progression than that of pure AD, and earlier studies of AD suggested extrapyramidal features and psychosis are predictors of decline (13,48,97–100). Some recent data, however, shows no difference in rate of cognitive decline between DLB and AD (101,102). In an autopsy study with patients who were part of the Florida Alzheimer's Disease Initiative Brain Bank, there was a shorter duration of illness for DLB compared to AD (63). In a longitudinal study of 63 DLB and 252 AD patients, psychometric performance and clinical staging methods did not distinguish groups in terms of rate of cognitive decline, but DLB is associated with increased risk of mortality. Extrapyramidal signs were strong predictors of mortality (103).

Description and distribution of pathology in DLB

Lewy bodies are concentric, intra-cytoplasmic neuronal inclusions that have long been a recognized pathology of brainstem monoaminergic and cholinergic nuclei in idiopathic Parkinson's disease (PD) (104,105). Subcortical Lewy bodies are distributed in the dorsal motor nucleus of the vagus, medullary magnocellular reticular nuclei, locus coeruleus, raphe nucleus, midbrain tegmentum, hypothalamus and basal forebrain (106–109). Neocortical Lewy bodies are less eosinophilic, less circumscribed, and are better detected by ubiquitin, but particularly by α-synuclein immunohistochemistry, which is now considered the gold standard (106). The limbic and temporal regions are particularly vulnerable to "cortical" Lewy bodies, with lesser involvement of frontal and posterior cortical regions (108–111). Spongiosis is also observed in the amygdala and basal forebrain (106). Similarly, using magnetic resonance imaging (MRI), the rates of whole brain atrophy and ventricular expansion over a 1 to 2 year interval do not differ between a sample of DLB later confirmed by autopsy and normal controls (112). When compared to AD, MRI voxel based

morphometry reveals that DLB has very little cortical involvement but does show a discrete cluster of grey matter loss in the cholinergic-rich regions of the nucleus basalis of Meynert in the basal forebrain and dorsal midbrain (113).

Lewy neurites (LN) are widespread alpha-synuclein positive inclusions that are located in neural processes, and preferentially affect limbic and temporal lobe structures (37,38,107).

A proportion of DLB cases have AD-type pathology that include neurofibrillary tangles (NFTs) and neuritic plaques (3,4,13). Plaques are composed of extracellular beta-amyloid (Ab) protein deposits comprised of 40 and 42 amino acid peptides. The neuritic plaques that accompany AD include a dense core of Ab40 with neuritic processes composed of the protein tau (114). In contrast, plaques in Lewy body disease are typically diffuse (though some may contain a core), and are primarily composed of Ab42 with a paucity or absence of tau-positive neuritis (115–119). Diffuse plaques are also numerous in brains of cognitively normal elderly (37,120,121). Most clinico-pathologic studies of DLB and AD do not take this distinction into account, and as such, it is not known whether differences in plaque-type influence clinical presentation. When NFTs are present in Lewy body disease, they are far less frequent than in AD, and regional distribution using Braak staging is often at Braak IV or less indicating confinement to limbic regions (3,47,122–125). Clinical diagnostic accuracy of DLB is significantly better in those with low Braak stages and lower tangle density (126,127).

Clinico-pathologic correlates in DLB and AD

Dementia severity is not associated with neocortical plaque density but is related to NFT burden in AD (123,128,129). In DLB, LB density but not plaque or NFT density is correlated with dementia severity (123,130,131). LN density has also been associated with the degree of cognitive impairment in DLB (132), suggesting that these inclusions may interfere with neuronal function, but further investigation is needed.

In AD, the CA1 region and subiculum of the hippocampus are severely affected while the CA2/3 region is considered the “resistant zone” and is typically spared (133–135). In DLB it is the CA2/3 region that is affected while the CA1 and subiculum regions are typically spared (37,136). Similarly, AD is associated with a near total loss of perforant pathway neurons while in DLB, the perforant pathway is more comparable to that of normal controls (137). Although damage to the CA1 region has been associated with memory impairment, is not known whether CA2/3 pathology affects memory function.

The ventral temporal lobe is heavily burdened by prominent Lewy body pathology and spongiosis (48,106). This neuroanatomic pattern appears to occur well before the onset of Lewy body pathology in other cortical regions, including the parietal lobe (110). Thus, early specific visual perceptual deficits may be associated with disruption of the pattern/object recognition pathway. Patients with VH have higher LB densities in amygdala, parahippocampus and inferior temporal cortex (136), suggesting the involvement of these regions in the development of VH. Nonetheless, VH can and do occur in patients with limbic only pathology (63).

The cholinergic hypothesis fits DLB better than AD

The use of new cholinergic toxins to selectively target the nucleus basalis of Meynert (which is 90% cholinergic and widely projects to the cortex) (138) reveals no impairment of memory, but does reveal deficits in sustained and divided attention (139–143). In addition, profound cholinergic neuronal loss and severely depleted choline acetyltransferase levels occur early in DLB disease course, while AD and normal controls show little difference

until the advanced stage of dementia (144–147). In addition, anticholinergic agents can elicit hallucinations and disturbed consciousness that vary as a function of cholinergic deficiency (148–153). Not surprisingly, one hypothesized mechanism for fluctuations and visual hallucinations in DLB includes cholinergic depletion of the basal forebrain alone (5,145,149,154). Increasing acetylcholine availability with cholinesterase inhibitors improves attention, hallucinations and alertness in early DLB (154–159). Thus, cholinergic depletion is a critical factor in the symptom manifestation of early DLB but may be less so in early AD. This highlights the importance of differentiating between early versus late stages of different dementias, since patients with advanced AD may have similar clinical features as those with early DLB.

Pharmacologic treatment of DLB

When faced with a challenging behavior, it is critical to first evaluate for potential medical contributors (e.g., pain, medication side effects, injury, underlying sleep disorder, depression, dehydration, metabolic disturbance), and treat accordingly.

Neuroleptic medication is frequently administered to dementia patients for episodic confusion, hallucinations, delusions and agitation (160,161). These clinical features are commonly observed in DLB, but there is convincing evidence that patients with DLB can harbor neuroleptic sensitivity to traditional and to some atypical neuroleptics (59,162–166). Specifically, antipsychotic agents with D2 antagonism and anticholinergic properties precipitate and/or exacerbate extrapyramidal signs and cognitive impairment, respectively (167,168). Unfortunately, discontinuation of the neuroleptic does not necessarily lead to a reversal of the adverse reaction (59). There is a mixed literature on the relationship between atypical antipsychotics and cognition, though the effects of quetiapine appear to be better in DLB than in AD (169–174). Olanzepine does not seem to worsen parkinsonism (169), though its anticholinergic properties may exacerbate cognitive impairment (172).

Levodopa-carbidopa is generally well tolerated in DLB, but response may not be at the magnitude in some patients as seen in patients with PD (51). There are reports of levodopa-carbidopa having a positive impact on cognition (175,176).

Brain acetylcholine is profoundly depleted in the early stages of DLB compared to AD (5,145–147). This is concerning because drugs with anticholinergic properties are often prescribed to the elderly to treat mood, psychosis, movement disorders, incontinence and pulmonary disease (150). Several studies have clearly demonstrated adverse reactions to anticholinergic agents that mimic delirium (151–153,177). Alternately, improvement (sometimes dramatic) in delirium-like or fluctuating symptoms (including VH) can occur with the use of cholinesterase inhibitors(146,178–181). Studies of cholinesterase inhibitors (182–184) reveal improved cognition in DLB and AD, and detrimental effects when suddenly withdrawn (185). A comparison of 30 DLB and 40 PDD with donepezil revealed improved MMSE scores by a mean of 3.9 points in the DLB group and by 3.2 points in PDD by 20 weeks.(186) Extrapyramidal side effects of cholinesterase inhibitors are actually quite low, and it is recommended as a first-line treatment for DLB (187).

The goals of therapy for RBD are to minimize the injuries to patients and their bedpartners and to reduce the likelihood of disrupted nighttime sleep. Clonazepam at a very low dose (0.25 to 0.5 mg at night) is usually effective (188). Melatonin may also be effective at 3 to 12 mg per night, either as monotherapy or in conjunction with clonazepam (189).

Excessive daytime sleepiness is challenging and the first approach is to try to identify whether the cause may be a medication side effect, mood or a primary sleep disorder. Although psychostimulants would be expected to exacerbate hallucinations and delusions in

DLB, experience has shown that daytime somnolence in some patients can be managed with agents such as modafinil and methylphenidate (190).

Non-pharmacologic treatment

Behaviors should be recognized as a form of communication and not as random, unpredictable or meaningless events. It may be helpful to determine which situations the behavior tends to occur (who is present, when does it happen, what makes it better or worse, what maintains it), and to focus on the emotion that accompanies the behavior. For example, aggressive behavior often represents frustration, fear, pain, a reaction to feelings of not being taken seriously or even mirroring of caregiver's behavior (i.e., impatience, agitation). Addressing these feelings may help to alleviate the patient's agitation.

In terms of non-medical interventions, managing challenging behaviors should be shifted from trying to change the patient to modifying other factors that may be causing or exacerbating the problem (191). Put differently, the patient cannot change, and therefore, it is up to those around him to change. This includes modifying the environment (e.g, reducing clutter, modifying illumination, reducing distracting noise), how we respond to behavior (e.g., validating the patient's concerns, apologizing, reassuring the patient, avoid correcting or quizzing the patient, model calm, avoid trying to "reality orient"), examining task demands (e.g., providing structure and routine, providing repetitive tasks, providing exercise, breaking down tasks into more manageable parts, focus on successes and not failures, refrain from giving tasks that are too hard).

Before treating hallucinations or delusions (false beliefs), it must be determined whether these symptoms are actually harmful or distressing to the patient. Educating the family member about ways to cope with these behaviors include encouraging them to validate the patient's feelings and devising strategies that 'go along' with the behavior (e.g., checking the house for intruders, appearing to call somebody to see what time is check-out time), that provide reassurance, and that does not involve arguing or trying to reason with the patient.

Providing information for the caregiver is an important part of helping to manage challenging behaviors. Psychoeducation intervention groups for caregivers have been associated with significant improvements in agitation and anxiety for dementia patients (192). Utilizing available support services, including adult day programs and companion services have also been shown to reduce caregiver related stress and reported feelings of overload, strain, depression and anger (193).

Conclusions

Clinical features that may be helpful in distinguishing early DLB from AD include neurocognitive presentation, visual hallucinations, extrapyramidal signs, fluctuations, neuroleptic sensitivity, REM sleep behavior disorder and dysautonomia. Early and accurate detection of DLB has implications for symptom management and for providing education and support to DLB patients and their caregivers.

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Table 1

Revised criteria for the clinical diagnosis of Dementia with Lewy bodies (DLB)

1	Central feature (essential for a diagnosis of possible or probable DLB)
	• Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or 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, executive function and visuospatial ability may be especially prominent.
2	Core features (2 core features are sufficient for a diagnosis of probable DLB, 1 for possible DLB.
	• Fluctuating cognition with pronounced variation in attention and alertness.
	• Recurrent visual hallucinations that are typically well formed and detailed.
	• Spontaneous features of parkinsonism
3	Suggestive features (if 1 or more of these is present in the presence of one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features is sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggested features alone.)
	• REM sleep behavior disorder
	• Severe neuroleptic sensitivity
	• Low dopamine transporter uptake in the basal ganglia demonstrated by SPECT or PET imaging

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