

# Clinical presentation and differential diagnosis of dementia with Lewy bodies: a review

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**Background:** Dementia with Lewy bodies is one of the most prevalent dementia diagnoses. However, differential diagnosis between dementia with Lewy bodies, Alzheimer's disease, and Parkinson's disease with dementia can still be very difficult given the overlap in neuropathology, clinical presentation, cognitive, and neuroanatomical changes.

**Method:** A literature review of dementia with Lewy bodies, Alzheimer's disease, and Parkinson's disease with dementia was conducted using PubMed.

**Results and Implications:** Accurate diagnosis of dementia with Lewy bodies is crucial in order to more accurately predict the progression of the disease and negative side effects from pharmacological treatment. The differences and similarities between dementia with Lewy bodies, Alzheimer's disease, and Parkinson's disease with dementia are highlighted in order to aid clinicians in differential diagnosis. Copyright © 2013 John Wiley & Sons, Ltd.

**Key words:** dementia with Lewy bodies; alpha synucleins; dementia; differential diagnosis; aging

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Dementia with Lewy bodies (DLB) is estimated to occur in 0% to 5% of the general population and constitute between 0% and 30.5% of cases of dementia, suggesting that DLB is the second most common dementia after Alzheimer's disease (AD) (Zaccai *et al.*, 2005). However, despite its prevalence, diagnosing DLB can be difficult because of overlapping symptoms between DLB, AD, and Parkinson's disease with dementia (PDD) (Nervi *et al.*, 2011). Given how critical accurate diagnosis is in treating dementia, this paper aims to present a detailed description of DLB, including pathology, clinical presentation, and treatment options. Additionally, we aim to highlight various similarities and differences between DLB and other types of dementia (specifically AD and PDD) in order to help clinicians and caregivers better distinguish between DLB and other neurological disorders and diseases.

## Clinical presentation of dementia with Lewy bodies

The three core symptoms associated with DLB include fluctuating cognition, recurrent visual hallucinations,

and Parkinsonism. A diagnosis of DLB can be made when at least two core features, or one core feature and one suggestive feature, are present (McKeith and Cummings, 2005; Whitwell *et al.*, 2007). Cognitive fluctuations are sudden changes in cognition, attention or arousal, and are one of the core symptoms of DLB (Ferman *et al.*, 2004; Tarawneh and Galvin, 2007). Other core features of DLB include visual hallucinations and Parkinsonism. An international, multi-center trial revealed that prevalence of recurrent visual hallucinations ranged from 69.6% to 85.7% in patients with DLB (Del Ser *et al.*, 2000). Spontaneous Parkinsonism is estimated to occur in between 60% and 92% of patients with DLB (Zupancic *et al.*, 2011). Extrapyrimal motor symptoms may include bradykinesia, rigidity, resting tremor, and postural instability (McKeith *et al.*, 2004). However, there is a lower prevalence of resting tremor relative to postural instability, stooped posture, and ataxia in DLB (Zupancic *et al.*, 2011).

Rapid eye movement sleep behavior disorder (RBD) may be a suggestive feature of DLB, in addition to various other neurodegenerative disorders (Jennum

*et al.*, 2013; Postuma *et al.*, 2013). RBD tends to occur during prodromal periods of DLB or early within the disease (Iranzo *et al.*, 2013). Iranzo *et al.* (2013) investigated 44 individuals with RBD and found that RBD often precedes the onset of both Parkinson's disease (PD) and DLB, suggesting that RBD may be useful in early diagnosis of Lewy body diseases (Iranzo *et al.*, 2013).

### Neuropathology of dementia with Lewy bodies

Dementia with Lewy bodies and other Lewy body diseases are characterized by the presence of Lewy bodies (Stubendorff *et al.*, 2012). Further, the presence of Lewy bodies, or abnormal aggregates of the protein alpha-synuclein, is necessary at autopsy to confirm a diagnosis of DLB (Zupancic *et al.*, 2011). Lewy bodies are most often found in the brainstem, specifically in the substantia nigra and locus coeruleus in individuals with DLB (McKeith *et al.*, 2005). Lewy bodies can also be found in the limbic system (e.g., amygdala), various cortical areas (e.g., frontal, cingulate, and inferior temporal cortices), and occasionally in the peripheral nervous system (Collerton *et al.*, 2003; Zupancic *et al.*, 2011; Nakatsuka *et al.*, 2013) in DLB.

### Imaging results

Cortical and subcortical atrophy is often seen in DLB (Forstl *et al.*, 1993; Donnemiller *et al.*, 1997; Burton *et al.*, 2002; Ceravolo *et al.*, 2003). Greater gray matter atrophy in temporal, frontal, and parietal lobes as well as the insular cortex has been noted in DLB relative to healthy controls (Burton *et al.*, 2002). Further, volume loss has also been found in subcortical regions, in particular, the amygdala and hippocampus (Burton *et al.*, 2002). However, relative to other areas of atrophy in DLB, and relative to individuals with AD, the temporal lobe and the hippocampus are generally preserved (Hashimoto *et al.*, 1998). Dopamine transporter studies have also revealed volume loss in other subcortical regions, such as the basal ganglia. More specifically, there tends to be degeneration of neurons in the substantia nigra (Donnemiller *et al.*, 1997; Walker *et al.*, 1999; Ceravolo *et al.*, 2003).

Reduced cerebral blood flow in the parietal and temporal regions has been found in DLB relative to healthy controls (Lobotesis *et al.*, 2001; Ballard *et al.*, 2002; Colloby *et al.*, 2002; Hanyu *et al.*, 2005). Studies have also found occipital hypoperfusion in DLB relative to healthy controls, which has been linked to visual hallucinations typical of DLB (Ishii *et al.*, 1998; Burton *et al.*, 2002; Ceravolo *et al.*, 2003).

### Neuropsychological performance

Individuals with DLB often present with various neuropsychological impairments. Perhaps the most commonly impaired domain is visuospatial functioning (Johnson *et al.*, 2005). Impairment in executive functioning has also been noted in DLB, particularly in the domain of attention; however, decline in word fluency, inhibition, and planning has also been noted (Guidi *et al.*, 2006; Mondon *et al.*, 2007). Memory, however, is often not as severely impaired as with other types of dementia. Further, memory tends to decline relatively late in the course of DLB (Zupancic *et al.*, 2011).

### Diagnostic issues

Diagnosis can present a variety of problems, in part, because it is often difficult to obtain an accurate and detailed history from patients with dementia. This can be a result of cognitive, behavioral, and neuropsychiatric symptoms (McKeith and Cummings, 2005). Therefore, diagnostic assessments often benefit from reports by the individuals' primary caregiver and other informants (Cordell *et al.*, 2013). Additionally, neuroimaging techniques can be useful when used collaboratively with clinical judgment and patient interviews, in order to rule out other neurological problems (e.g., cerebral infarction) that can alter cognitive abilities but do not warrant a diagnosis of dementia (Zupancic *et al.*, 2011; Nakatsuka *et al.*, 2013).

Diagnostic issues in DLB extend beyond dealing with general cognitive decline. Fluctuating cognition, which is estimated to be prevalent in between 30% and 89% of patients, presents a relatively unique (although not exclusive) problem in diagnosing DLB (Del Ser *et al.*, 2000; Serby and Samuels, 2001). Fluctuations in cognition may present problems if clinicians see patients, and they perform similarly to their baseline functioning (Zupancic *et al.*, 2011). This again highlights the utility of caregiver reports (McKeith *et al.*, 1996).

One of the greatest difficulties in diagnosing DLB is the presence of overlapping features between DLB and other dementias, including AD and PDD (Nervi *et al.*, 2011). Improvement in diagnostic accuracy is critical given the potential for differential adverse side effects from neuroleptic medication (Mori, 2000; Whitwell *et al.*, 2007). However, some notable differences may aid in proper diagnosis and treatment by clinicians. Therefore, we have outlined some important distinctions in clinical presentation, neuropathology,

neuroimaging, and neuropsychological test performance between DLB and AD and DLB and PDD.

## Dementia with Lewy bodies and Alzheimer's disease

### Clinical presentation

Dementia with Lewy bodies has several overlapping features with AD (Zaccai *et al.*, 2005; Kaur *et al.*, 2013; Swerdlow and Newell, 2012). However, the three core clinical features of DLB often help distinguish the two disorders. For example, relative to patients with AD, patients with DLB are more likely to demonstrate visual hallucinations and extrapyramidal tract signs (e.g., bradykinesia, masked face, and postural instability). Patients with AD may occasionally demonstrate similar symptoms to DLB (e.g., Parkinsonism symptoms). Kaur *et al.* (2013) found that, using the Unified Parkinson's Disease Rating Scale, the presence of masked face was the best way to differentiate between DLB and AD. Although some similar features, such as extrapyramidal tract signs, may be present later in the progression of AD, they are often early clinical features of DLB (Kaur *et al.*, 2013; Yoshizawa *et al.*, 2013). Additionally, individuals with DLB are more likely to experience fluctuations in cognition relative to patients with AD. Caregivers of patients with DLB report increased periods of staring into space without demonstrating engagement with the environment relative to caregivers of patients with AD (Zupancic *et al.*, 2011).

Another clinical feature that is useful in differentiating between DLB and AD is autonomic dysfunction. Patients with DLB are more likely to experience incontinence, constipation, and orthostatic hypotension relative to patients with AD (Allan *et al.*, 2007). Further, at least some of the core features in DLB, such as fluctuating cognitions and repeated falls, may at least in part result from problems with autonomic functioning. It has been proposed that orthostatic hypotension and constipation are more prevalent in patients with DLB (and other Lewy body diseases) because of the presence of Lewy bodies in brain regions such as the locus coeruleus (Kovari *et al.*, 2009). Patients with DLB also often show increased depressive symptoms, even after controlling for cognitive decline, relative to patients with AD (Yamane *et al.*, 2011).

### Neuropathological differences

Patients with DLB often have Lewy bodies and in both the brain stem and cortex. Although the presence of

Lewy bodies at the time of autopsy is necessary to confirm a diagnosis of DLB, it is important to note that similar neuropathology may also be found in patients with AD (Harding *et al.*, 2002; Stubendorff *et al.*, 2012). Further, there may also be a presence of AD pathology (e.g., neurofibrillary tangles and beta-amyloid plaques), in addition to Lewy bodies, in patients with DLB (Dickson *et al.*, 1987; Josephs *et al.*, 2004). This overlap suggests that neuropathology may not be the best way to distinguish between AD and DLB, and that they may actually be different presentations of the same underlying disorder (Swerdlow and Newell, 2012).

### Imaging results

There have been mixed findings regarding neuroanatomical differences between DLB and AD. For example, some studies show similar patterns of gray matter loss in patients with AD and DLB (Barber *et al.*, 2000; Burton *et al.*, 2002; Almeida *et al.*, 2003; Cousins *et al.*, 2003; Ballmaier *et al.*, 2004). However, several other studies have found differences in gray matter and white matter volumes between patients with DLB and AD (Table 1). More specifically, several studies show that patients with DLB have less gray matter atrophy than patients with AD in the medial temporal lobe (Hashimoto *et al.*, 1998; Burton *et al.*, 2002; Ballmaier *et al.*, 2004; Burton *et al.*, 2004; Tam *et al.*, 2005; Whitwell *et al.*, 2007). It is important to note that variable results may at least, in part, be due to differences other than underlying pathology, such as progression of the disease or severity of symptoms (Whitwell *et al.*, 2007).

Research findings also document differences between AD and DLB in subcortical volume. In particular, relative to AD, patients with DLB have increased atrophy in subcortical gray matter (e.g., putamen and basal forebrain) and white matter (e.g., dorsal midbrain

Table 1 Comparison of neuroanatomical differences between dementia with Lewy bodies and Alzheimer's disease

	Diagnosis	
	DLB	AD
Gray matter		
Medial Temporal Lobe		Greater atrophy
Putamen	Greater atrophy	
Basal forebrain	Greater atrophy	
White matter		
Dorsal midbrain	Greater atrophy	
Pons	Greater atrophy	

DLB, dementia with Lewy bodies; AD, Alzheimer's disease.

and pons) (Cousins *et al.*, 2003; Brenneis *et al.*, 2004; Hanyu *et al.*, 2005; Nakatsuka *et al.*, 2013). Nakatsuka *et al.* (2013) found that midbrain atrophy was the best way to discriminate DLB and AD.

Additionally, I-Metaiodobenzylguanidine (mIBG) scintigraphy has recently been used in the differential diagnosis of DLB from AD (Fujishiro *et al.*, 2012). mIBG scintigraphy can help identify cardiac sympathetic denervation, which has been shown in DLB (even in the prodromal state) but not AD (McKeith *et al.*, 2005; Fujishiro *et al.*, 2010). Therefore, mIBG demonstrates promise in helping differentiate between DLB and AD.

### Neuropsychological differences

Some studies have demonstrated that there are similar rates of cognitive decline in individuals with AD, DLB, and people with both AD and DLB pathology (Johnson *et al.*, 2005). However, others studies suggest that patients with DLB often have greater impairment in functioning at the earlier stages of the disease compared with individuals with AD suggesting more rapid decline (Zupancic *et al.*, 2011). Although impairments in multiple cognitive domains are often present in both DLB and AD, there are often distinct patterns of performance that may help differentiate between the two diseases (Table 2).

Typically, patients with DLB show greater impairment in visuospatial functioning (orientation, construction, perception, and memory), measures of attention (sustained, selective, and divided attention), and executive abilities relative to individuals with AD (Calderon *et al.*, 2001; Collerton *et al.*, 2003; Johnson *et al.*, 2005; Guidi *et al.*, 2006; Nervi *et al.*, 2008;

Yoshizawa *et al.*, 2013). Collerton *et al.* (2003) conducted a meta-analysis of the literature on neuropsychological differences between patients with AD and DLB, and found that differences on measures of attention, executive functioning, and visuospatial ability yielded large effect sizes. Another study showed that patients with DLB consistently performed worse on various measures of attention and other executive abilities. In fact, only one patient in the DLB sample ( $N=10$ ) was able to complete the Wisconsin Card Sorting Test (Calderon *et al.*, 2001). Additionally, deficits in attention and other executive functions may, in part, be attributable to the fluctuations in cognition frequently observed in DLB.

There is often greater impairment in memory in individuals with AD relative to DLB, and memory deficits might not show up until the later stages of DLB. Although both groups typically perform worse on memory tasks relative to healthy controls, there are frequently significant differences in performance between DLB and AD groups such that there is greater impairment in individuals with AD (Calderon *et al.*, 2001; Guidi *et al.*, 2006). Calderon *et al.* (2001) found that both the AD and DLB group were impaired in their ability to recall words and faces; however, patients with AD performed significantly worse on immediate recall, delayed recall, and recognition trials of a test of memory for stories. Additionally, patients with AD showed significantly greater impairment on a prose memory test relative to patients with DLB (Guidi *et al.*, 2006). However, consistent with previous findings that visuospatial ability is more severely impaired in individuals with DLB (Calderon *et al.*, 2001; Collerton *et al.*, 2003; Guidi *et al.*, 2006), visuospatial memory performance has been demonstrated to be worse in individuals with DLB relative to individuals with AD (Calderon *et al.*, 2001).

Table 2 Comparison of the severity of neuropsychological impairment between dementia with Lewy bodies and Alzheimer's disease

Neuropsychological performance	Diagnosis	
	DLB	AD
Memory		Greater impairment
Visuospatial ability	Greater impairment	
Attention	Greater impairment	
Processing speed	Greater impairment	
Executive functioning	Greater impairment	

DLB, dementia with Lewy bodies; AD, Alzheimer's disease.

## Dementia with Lewy bodies and Parkinson's disease with dementia

### Clinical presentation

Differentiation between DLB and PDD can be very difficult given the similarities in motor, psychiatric, and cognitive problems (Ballard *et al.*, 2002; Aarsland *et al.*, 2003; Noe *et al.*, 2004). Distinguishing between the two depends on the onset of the cognitive and motor symptoms in relation to one another (Aarsland *et al.*, 2003; Mondon *et al.*, 2007). When cognitive impairments or hallucinations occur before, or within one year of the onset of Parkinsonism, patients are

typically diagnosed with DLB. However, when Parkinsonism precedes dementia by more than a year, there is usually a diagnosis of PDD (Aarsland *et al.*, 2003; Mondon *et al.*, 2007). However, it is important to note that because many symptoms can be gradual, it is difficult to differentiate between DLB and PDD in clinical practice (Zupancic *et al.*, 2011; Nakatsuka *et al.*, 2013).

#### Neuropathological differences

Both DLB and PDD involve accumulation of Lewy bodies in addition to cholinergic deficits. Therefore, some have proposed that there may be a single pathology (Lewy body diseases), which can manifest in different ways clinically (Aarsland *et al.*, 2003; Lippa *et al.*, 2007; Nakatsuka *et al.*, 2013). Further, Lewy bodies are often found in the same cortical and subcortical regions in PDD and DLB. For example, Lewy bodies tend to aggregate in various regions of the brainstem (e.g., locus coeruleus), the basal ganglia, and cortical areas (Vernon *et al.*, 2010). Although both DLB and PDD patients may have comorbid AD pathology (Ballard *et al.*, 2006), research suggests that individuals with DLB are more likely to have AD pathology in addition to Lewy bodies when compared with individuals with PDD. This may indicate that there is a higher probability of comorbid AD in DLB than in PDD or that these have distinct underlying pathologies (Andersson *et al.*, 2011).

#### Imaging results

Neuroimaging, in particular, magnetic resonance imaging and diffusions tensor imaging, have not been very effective in distinguishing between DLB and PDD (Vernon *et al.*, 2010). Differences in the amount of cerebral atrophy between individuals with PDD and DLB are often undetectable, despite the fact that both involve cortical and subcortical neurodegeneration (Aarsland *et al.*, 2003; Burton *et al.*, 2004). Subcortical atrophy is typically observed within the nigrostriatal system and locus coeruleus in both cases (Wolters and Braak, 2006). O'Brien *et al.* (2004) also found that dopamine transporter studies may not be effective in distinguishing between DLB and PDD. Although other studies have found greater cortical atrophy in the temporal, parietal, and occipital lobes of patients with DLB relative to those with PDD (Beyer *et al.*, 2007), it appears that, generally, neuroimaging studies may not be that useful in differential diagnosis.

#### Neuropsychological differences

Neuropsychological deficits in DLB are also similar to those seen in PDD (Zupancic *et al.*, 2011); however, individuals with DLB often show greater impairment on measures of processing speed, visuospatial abilities, visuospatial memory, executive functioning, and attention (Aarsland *et al.*, 2003; Mondon *et al.*, 2007; Filoteo *et al.*, 2009; Kao *et al.*, 2009). For example, Mondon *et al.* (2007) found that patients with DLB performed significantly worse than those with PDD on measures of processing speed, inhibition, and memory, even when groups did not differ on Mini mental status exam or Mattis dementia rating scale scores. Further, groups did not differ on motor symptoms or proportion of patients being treated with various medications (cholinesterase inhibitors, antidepressives, or neuroleptic medications) (Mondon *et al.*, 2007). Other studies have shown that patients with DLB perform worse on measures of verbal learning and memory as well relative to patients with PDD (Filoteo *et al.*, 2009). Therefore, although patterns of impairment are similar, several studies suggest that impairment is often greater in DLB than in PDD (Table 3).

#### Prognosis and recommended treatment

Prognosis for DLB is relatively poor (Zupancic *et al.*, 2011). Length of survival after diagnosis is variable; however, one study found that the median time of survival for individuals with DLB is around 5 years after the onset of symptoms (Jellinger *et al.*, 2007). Another study found that median survival is roughly 7 years after receiving a diagnosis of DLB (Williams *et al.*, 2006). These suggest a relatively increased rate of progression in DLB relative to AD (Williams *et al.*, 2006; Zupancic *et al.*, 2011).

Cognitive problems are thought to be related to cholinergic and glutamatergic changes in DLB

Table 3 Comparison of the severity of neuropsychological impairment between dementia with Lewy bodies and Parkinson's disease with dementia

Neuropsychological performance	Diagnosis	
	DLB	PDD
Memory	Greater impairment	
Visuospatial ability	Greater impairment	
Attention	Greater impairment	
Processing speed	Greater impairment	
Executive functioning	Greater impairment	

DLB, dementia with Lewy bodies; PDD, Parkinson's disease with dementia.

(Emre *et al.*, 2010; Zupancic *et al.*, 2011). Therefore, treating cognitive symptoms with cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists may be beneficial in the management of symptoms (Emre *et al.*, 2010). Memantine (an NMDA receptor antagonist) has been used in the treatment of DLB. Relative to those in the placebo group, patients showed greater improvement in clinical and behavioral symptoms (Emre *et al.*, 2010). Cholinesterase inhibitors (e.g., Donepezil) have also demonstrated efficacy in reducing both neuropsychiatric and cognitive symptoms in DLB (Zupancic *et al.*, 2011). However, other studies have shown that cholinesterase inhibitors are not efficacious in DLB. Rolinski *et al.* (2012) reviewed several studies evaluating the efficacy of cholinesterase inhibitors in DLB, PD, and PDD and found that dropout rates and dropouts due to adverse events were higher in treatment groups relative to groups receiving a placebo. Therefore, providers should be aware of individuals' ability to tolerate these medications when prescribing pharmacological agents for the treatment of cognitive symptoms.

Mood symptoms, particularly anxiety and depression, are frequently present in DLB. Symptoms are typically treated with selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors (McKeith *et al.*, 2005). Further, it is important to note potential contraindications given other cognitive and neuropsychiatric symptoms. For example, tricyclic antidepressants should not be administered to individuals with DLB because of their anticholinergic properties, which can exacerbate the cognitive and other neuropsychiatric symptoms (e.g., visual hallucinations) (Zupancic *et al.*, 2011).

Despite pharmacological treatment options for cognitive and mood symptoms, treatment can be particularly difficult in the case of motor symptoms and visual hallucinations in patients with DLB. Individuals with PDD often treat motor symptoms with antiparkinsonian drugs (e.g., L-dopa) (Zupancic *et al.*, 2011). However, individuals with DLB are less likely to respond to antiparkinsonian drugs than those with PD (Molloy *et al.*, 2005), and they may actually result in the development or exacerbation of psychotic symptoms (Molloy *et al.*, 2005; Zupancic *et al.*, 2011). Given the contraindications of prescribing dopaminergic drugs, nonpharmacological interventions are typically utilized in DLB. Mobility aids (e.g., walkers), in addition to physical therapy, are recommended to help prevent falls (Zupancic *et al.*, 2011). Primary care physicians also often provide antipsychotics to treat the visual hallucination that often accompany DLB; however, antipsychotics can result in increased rigidity

and bradykinesia (Zupancic *et al.*, 2011). Antipsychotics have also been associated with other adverse effects, such as orthostatic hypotension (Gugger, 2011), which can be particularly problematic given individuals with DLB are already at increased risk for orthostatic hypotension (Allan *et al.*, 2007). Further, the Food and Drug Administration has placed a black box warning on second-generation antipsychotics for patients with dementia (Zupancic *et al.*, 2011).

Given the relatively poor prognosis of patients with DLB and the presence of cognitive, affective, motor, and neuropsychiatric symptoms, it is important to consider the implications of treating each symptom. Specifically, it is essential that clinicians understand the impact that pharmacological interventions may have. Additionally, although various treatments are available to help ameliorate symptoms associated with DLB, they do not cure them. This highlights the importance in early and accurate diagnosis of DLB, in order to prevent adverse drug effects from inappropriate treatment.

### Conflict of interest

None declared.

### Key points

- Despite its prevalence, diagnosing DLB can be difficult because of overlapping features (e.g., clinical presentation, neuropathology, neuroanatomy, and neuropsychological performance) between DLB, AD, and PDD.
- Accurate diagnosis is crucial given differences in progression, prognosis and treatment of the various disorders.
- The potential impact of inaccurate diagnosis highlights the importance of clinicians' awareness of similarities and differences between DLB and other types of dementia.

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