# Dementia with Lewy Bodies

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**Summary**

Dementia with Lewy bodies (DLB) is a neurodegenerative disease which is recognized as one of dementia following Alzheimer's disease (AD). The clinical presentation of DLB is across between AD and Parkinson's disease (PD). The major clinical symptoms in DLB include fluctuations in cognition, visual hallucinations and parkinsonism. The neuropathology of DLB illustrated with deposition of Lewy bodies in the cortex and subcortical areas of human brain. Nicotinic and muscarinic receptors have been found to be lower in many regions of brains affected by DLB compared to normal. Neuropsychiatric aspects present in DLB involve with changes in nicotinic and muscarinic receptors. So far, management of DLB with cholinesterase inhibitors is one of the most effective treatments. Many DLB patients respond well with improvements in clinical symptoms and quality of life as well as a low incidence of neuroleptic sensitivity reactions, a serious side effect of DLB therapy with antipsychotic drugs.

**Keywords**: Dementia; Lewy bodies; Nicotinic receptor; Muscarinic receptor; Therapy

## Introduction

Dementia with Lewy bodies (DLB) is one of the neurodegenerative dementia with higher prevalence in western than Asian population (Chan et al., 2002; Hou et al., 2006; Yamada et al., 2001). The disease was firstly recognized and described by Kosaka et al. (1984) as the term of "diffuse type of Lewy Bodies Disease". DLB has been reported to account for 0-5% of general population and for 15-25% of all cases of dementia (McKeith et al., 1992; Shergill et al., 1994). Incidence of DLB is estimated around 0.1% a year for the general population and 3.2% a year for all dementia patients. Nowadays, understanding of DLB is increasing with better differentiation from other neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). The clinical features and pathology of DLB overlap with AD and PD. The major clinical features include progressive dementia together with fluctuations in cognition, visual hallucinations and parkinsonism (Aarsland et al., 2001; Rockwell et al., 2000). Other clinical symptoms present to a lesser extent in DLB but not commonly seen in AD are auditory hallucinations, depression, and recurrent falls (McKeith & O'Brien, 1999). The presence or absence of each major feature contributes to clinical diagnosis of probable or possible DLB as explained in the consensus guidelines for the clinical and pathologic diagnosis of DLB (Table 1) (McKeith et al., 1996). Because neuroleptic sensitivity with substantial decline in motor skills and changes in mental status often occurs after antipsychotic medication is introduced for neuropsychiatric management in DLB, differential diagnosis from AD and DLB is very crucial.

## Neuropathology of dementia with Lewy bodies

The neuropathology of DLB is characterised by the presence of Lewy bodies diffused abundantly in the cortex and subcortical areas of human brain. In many DLB patients, the occurrence of Lewy bodies is frequently accompanied by varying degrees of Alzheimer pathology in the cerebral cortex and neuronal loss in the substantia nigra (Gurd et al., 2000; McKeith et al., 1996). However, paired helical filaments, hyperphosphorylated tau protein and neurofibrillary tangles, major neuropathological hallmarks in AD, are found at lower levels in DLB than AD (Hampel et al., 2004; Harrington et al., 1994). Deposition of Lewy bodies occurs primarily in subcortical region of brain involved with Parkinson's disease, whereas DLB is associated with abundant Lewy body pathology in temporal cortex and striatum. The occurrence of Lewy bodies and location of Lewy bodies deposition are the essential features that assist neurologists for pathological differential

diagnosis of DLB from AD and PD, although Lewy-related neurites, varying degree of Alzheimer pathology, neuronal loss in the brainstem nuclei and spongy change are also frequently seen (McKeith et al., 1996).

**Table 1** Consensus criteria for the clinical diagnosis of probable and possible DLB

A. 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 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.

B. Two of the following core features are essential for a diagnosis of probable DLB, and one is essential for possible DLB:
   a. Fluctuating 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.

C. 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.

D. A diagnosis of DLB is less likely in the presence of
   a. Stroke disease, evident as focal neuroleptic signs or on brain imaging
   b. Evidence on physical examination and investigation of any physical illness or other brain disorders sufficient to account for the clinical picture.

Lewy bodies (Figure 1) is the pathological hallmark of Lewy body diseases, including PD and DLB (Kosaka & Iseki, 2000). Lewy bodies are spherical intracytoplasmic eosinophilic neuronal inclusion bodies, either multilocular or fusiform (McKeith et al., 1996; McKeith et al., 2004), consisting of a central granular material and vesicular profiles and a peripheral intermediate filaments (Gai et al., 2000). The inclusion contains aggregated α-synuclein (Iseki et al., 2000; Lippa et al., 1998) which localises with ubiquitin, an amino-acid peptide that is conjugated to abnormal protein to signal protein degradation (Gai et al., 2000; Kuusisto et al., 2003). Normally, the α-synuclein is a 140-amino acid protein expressed at high levels in synaptic terminals but its physiological function remains largely unclear (Clayton & George, 1998). The α-synuclein is encoded by the alpha-synuclein gene localizing on human chromosome 4q21.3-q22 (Chen et al., 1995; Shibasaki et al., 1995). Several studies reported point mutations in the alpha-synuclein gene contributed to Lewy bodies formation in Lewy bodies diseases including PD and DLB. The mutations of α-synuclein at amino acids residue 53 from alanine to threonine (A53T) (Polymeropoulos et al., 1997) and residue 30 from alanine to proline (A30P) (Kruger et al., 1998) were discovered in familial PD whereas the substitution of glutamate to lysine at amino acid residue 46 (E46K) was evident in an autosomal-dominantly inherited form of DLB (Zarranz et al., 2004). These mutations cause self-aggregation of α-synuclein (Conway et al., 2000; Narhi et al., 1999) leading to acceleration of α-synuclein fibrillization and abnormal protein formation in Lewy bodies in DLB (Bayer et al., 1999; Campbell et al., 2000; Goedert, 1999; Kotzbauer et al., 2004). The lesions increase vulnerability of neuronal cells to toxicity and cell death induced by iron (Ostrerova-Golts et al., 2000) and oxidative stress (Kanda et al., 2000; Wersinger & Sidhu, 2003).

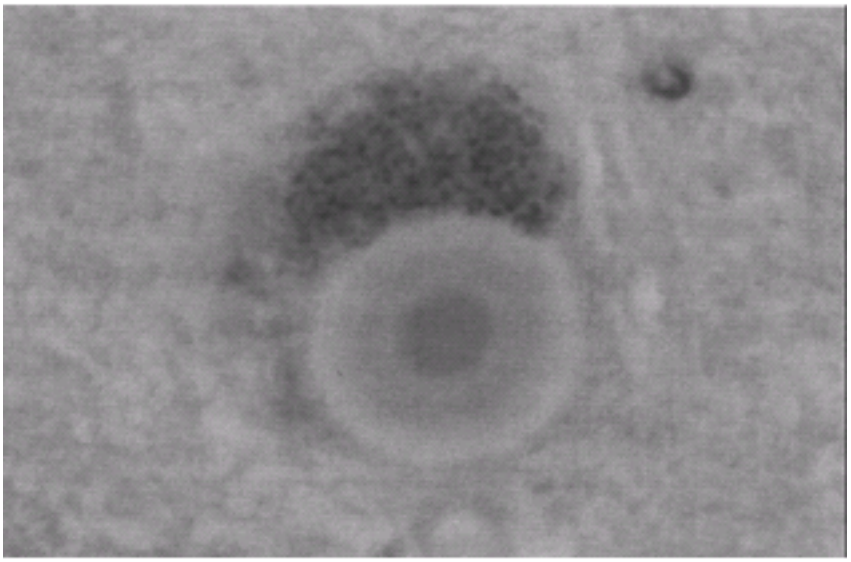

**Figure 1** Lewy bodies stained with hematoxylin and eosin. Lewy bodies are the intracytoplasmic, eosinophilic inclusions with a clear halo around in the neuron that contain brown neuromelanin.
*Source*.
Mirra & Hyman (2002).

## Cholinergic receptors in dementia with Lewy bodies

Autoradiography studies have shown alterations of nicotinic receptor binding in many brain regions of DLB patients. A significant loss of [$^{3}$H]nicotine binding, representing all nicotinic receptor binding, was present in the substantia nigra, dorsolateral tegmentum and the granular layer of hippocampus (Perry et al., 1995) whereas a reduction of 5-[$^{125}$I]-A-85380 binding, representing $\alpha_4$-nicotinic receptor binding, was evident in the substantia nigra and entorhinal cortex (Pimlott et al., 2004). [$^{125}$I] α-bungarotoxin representing $\alpha_7$-nicotinic receptor binding, [$^{3}$H]nicotine (Court et al., 1999), and 5-[$^{125}$I]-A-85380 (Pimlott et al., 2004) binding was also reduced in the reticular, dorsolateral and ventrolateral nuclei in the thalamus of DLB brains. In striatum, [$^{3}$H]nicotine (Court et al., 2000; Perry et al., 2000), [$^{3}$H]epibatidine representing $\alpha_3$- and $\alpha_4$-nicotinic receptor bindings (Martin-Ruiz et al., 2002) and 5-[$^{125}$I]-A-85380 binding (Pimlott et al., 2004) was significantly reduced in DLB compared to age-matched controls. In comparison with AD, [$^{3}$H]nicotine binding in parietal cortex was more extensively reduced in DLB (Perry et al., 2000). The lower binding in DLB compared to AD was also found in frontal cortex with [$^{125}$I] α-bungarotoxin binding (Rei et al., 2000). [$^{3}$H]epibatidine binding in temporal cortex of AD and DLB was significantly lower than in the controls (Martin-Ruiz et al., 2000). The decreased [$^{3}$H]epibatidine binding correlated with synaptophysin loss in both AD and DLB and decreased choline acetyltransferase enzyme (ChAT) in DLB (Rei et al., 2000).

Muscarinic receptors in DLB have been investigated to a lesser extent than nicotinic receptors and change in muscarinic receptors has been inconsistently reported in many studies. Muscarinic M1 immunoreactivity is extensively decreased in both cell bodies and dendrites of various neuronal cell types in the region of hippocampus of DLB brains (Shiozaki et al., 2001). Pirenzepine binding increased in the temporal and parietal neocortex of DLB patients and the increase correlated with experience of delusions (Ballard et al., 2000). Increased M1 receptors was also evident in the temporal cortex with increased M3 receptors in the frontal cortex and decreased M4 receptors in the temporal cortex of DLB brains (Odawara et al., 2003; Shiozaki et al.,1999). However, reduced pirenzepine binding was found in the striatum accompanied with increased M4 binding in insula and cingulate cortex and claustrum of DLB (Piggott et al., 2003).

**Neuropsychiatric symptoms in dementia with Lewy bodies**

Neuropsychiatric symptoms in DLB are clinical characteristics that can be distinguished from other neurodegenerative diseases. These symptoms are visual and auditory hallucinations and delusions (DelSer et al., 2000; Rockwell et al., 2000). Visual hallucinations are more frequent than PD (Aarsland et al., 2001) and more persistent in DLB than AD (Ballard et al., 2001) and present at early stage of the disease (Ballard et al., 1999). Visual hallucinations were appeared to associate with numerous Lewy bodies in the inferior temporal cortex, amygdala and parahippocampus (Harding et al., 2002), lowered $\alpha_7$-nicotinic receptor binding (Court et al., 2001) and ChAT (Perry et al., 1990; Ballard et al., 2000) as well as elevated M2 and M4 muscarinic receptor bindings (Teaktong et al., 2005) in the brains of DLB patients experiencing visual hallucinations. Because $\alpha_7$-nicotinic (Aztiria et al., 2004; Han et al., 2003), M2 (Erisir et al., 2001; Mrzljak et al., 1996) and M4 (Rossner et al., 1993) receptor proteins and mRNAs are localized in visual cortex and may influence visual processing, the alteration of these receptors could contribute to disturbances in vision in DLB. Auditory hallucinations are less common psychiatric symptoms in DLB (Aarsland et al., 2001) and less persistent than visual hallucinations in DLB patients (Ballard et al., 2001). Delusions occur more frequently in DLB than AD (DelSer et al., 2000; DelSer et al., 2001). These symptoms include Capgras' syndrome (the belief that similar-looking impostors have replaced relatives) (Marantz & Verghese, 2002), paranoid beliefs of persecution and theft and phantom boarder delusions (the belief that strangers live in the home) (Aarsland et al., 2001). The association between delusions and the cholinergic system is present with increased M1 muscarinic receptor binding in the temporal cortex (Ballard et al., 2000) and M2 muscarinic receptor binding in the cingulate cortex (Teaktong et al., 2005) of DLB patients with delusions. The association between increases in muscarinic receptors and delusions in DLB may explain efficacy of olanzapine, which exhibits antagonistic activity on muscarinic receptors (Lavalaye et al., 2001; Mulsant et al., 2004), in alleviating delusions in dementia patients.

**Pharmacotherapy of dementia with Lewy bodies**

Many drugs augmenting brain cholinergic activity have been introduced in clinical DLB therapy. Cholinesterase inhibitors which is a group of approved drugs for treatment of AD have been used to study effectiveness in DLB patients. Rivastigmine reduced neuropsychiatric symptoms including anxiety, delusions and hallucinations compared to placebo in DLB patients and sleep disturbances also improved during rivastigmine treatments (Maclean et al., 2001). Many patients who received rivastigmine illustrated improvement in attention and cognitive functions throughout period of rivastigmine treatments (Grace et al., 2001; McKeith, Grace, et al., 2000; McKeith, Ser, et al., 2000; Wesnes et al., 2002). Improvements in quality of life of the patients were noticed with more independence in mobility and the activities of daily living (Maclean et al., 2001). Donepezil demonstrated benefit in improvement in cognitive functions (Rojas-Fernandez, 2001; Samuel et al., 2000) of patients with DLB as well as remission of agitation and behavioural disturbances (Coulson et al., 2002; Fergusson & Howard, 2000; Lanctot & Herrmann, 2000). Galantamine also recently showed advantages in the improvement of cognitive functions, activities of daily living and sleep and reducing neuropsychiatric symptoms such as delusions, hallucinations, apathy and depression of DLB patients without adverse effect on parkinsonism although mild side effects such as nausea and anorexia occurred in few patients (Edwards et al., 2004). Theoretically, these cholinesterase inhibitors might produce deterioration of parkinsonism in DLB patients. However, improvement in parkinsonism was demonstrated in the patients treated with rivastigmine (McKeith, Grace, et al., 2000) and donepezil (Arahata et al., 2001). The possibility of this improvement might be involved with dopaminergic activity of these cholinesterase inhibitors in addition to increase in acetylcholine levels. Donepezil (Liang et al., 2006; Shearman et al., 2006) and rivastigmine (Liang et al., 2006) have recently been shown to increase release of dopamine in

the cortex, whereas galantamine increase release of dopamine in the striatum of rats (Zhang et al., 2004). The stimulation of nicotinic receptors in the striatum has illustrated to be responsible for dopamine release (Cao et al., 2005). The nicotinic and dopaminergic activities of cholinesterase inhibitors might be possible reasons for the efficacy in alleviating parkinsonism in DLB patients.

A major problem involved with DLB therapy is severe sensitivity to the extrapyramidal side effects (EPS) of antipsychotic drugs (Mendez & Lipton, 2001). Treatment with antipsychotic drugs, especially conventional drugs such as haloperidol, to relieve neuropsychiatric symptoms is contraindicated. Although atypical antipsychotic drugs might be safer and used as alternative agents, some of them should not be considered as first-line drug. Olanzapine showed significant reductions in delusions and hallucinations and improvement in quality of life of DLB patients (Cummings et al., 2002). Unfortunately, worsening of parkinsonian symptoms and an increase in confusion, agitation and hallucinations have been reported in DLB patients receiving olanzapine to improve psychotic symptoms (Coulson et al., 2002; Walker et al., 1999). Treatment with risperidone in DLB patients was also evident in severe neuroleptic sensitivity reactions in many case reports (McKeith et al., 1995; Sechi et al., 2000). Quetiapine showed positive effects in psychotic symptom treatment and a decrease of disruptive behavior in patients with DLB (Fernandez et al., 2002; Takahashi et al., 2003). However, side effects such as somnolence and orthostatic hypotension may be associated with quetiapine in DLB (Takahashi et al., 2003) and mild motor worsening has been also reported in some patients treated with quetiapine (Fernandez et al., 2002). The sensitivity to EPS of patients treated with atypical antipsychotic drugs seems to be associated with properties of the drugs on dopaminergic $D_2$-receptor profile. Olanzapine and risperidone display more potent in blocking $D_2$-receptor, determined by receptor dissociation constant, than quetiapine (Matsui-Sakata et al., 2005). The incidence of EPS of these antipsychotic drugs is positively consistent with their antagonistic effect at $D_2$-receptor (Tauscher et al., 2002). Therefore, cholinesterase inhibitors may be the safer and effective alternatives for the psychotic symptom management in DLB.

## Conclusions

DLB is one of neurodegenerative dementia which has α-synuclein pathology as a primary feature. The clinical symptoms of DLB are across between AD and PD and differentiation of DLB from those two diseases is based on diagnosis in neuropsychiatric symptoms and neuropathology. The cholinergic system plays a role in the clinical characteristics of DLB in particular the alterations of nicotinic and muscarinic receptors in the brain of DLB patients being associated with psychotic symptoms. Treatment of DLB is a challenge if clinical symptoms of patients are relieved without producing neuroleptic sensitivity. Cholinesterase inhibitor is the most appropriate group of drugs considered as effective agents in management of dementia and neuropsychiatric symptoms in DLB.

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