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Review Article

Diffuse Lewy body disease

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ABSTRACT

Diffuse Lewy body disease, also called dementia with Lewy bodies (DLB), is defined as progressive dementia and pathological Lewy bodies distributed in the central and autonomic nervous systems. The clinical features are dementia, cognitive fluctuations, visual hallucinations, parkinsonism, and REM sleep behavior disorder (RBD). Confirmatory techniques include dopamine transporter imaging, meta-iodobenzylguanidine (MIBG) myocardial scintigraphy, and polysomnography.

The pathology finding in DLB is misfolded alpha-synuclein, the main component of Lewy bodies, propagating in the central nervous system. This may interrupt the acetylcholine pathway and activate an inflammatory response. Mutations of several genes have been found in patients with DLB, including *SNCA*, *GBA*, and *APOE*.

The differential diagnosis of DLB and Parkinson's disease with dementia (PDD) is a debated issue. Clinical features distinguishing DLB from PDD include the timing of dementia and visual hallucinations, responses to dopaminergic agents and anti-psychotics, and imaging findings.

As to the management of DLB, cholinesterase inhibitors are the Level-A recommendation for treating dementia in DLB patients and also are beneficial for treating visual hallucinations and psychotic symptoms. Dopamine agonists have the risk of inducing psychotic symptoms, while levodopa should be used carefully for motor symptoms. Melatonin and clonazepam are effective in controlling RBD. Several other treatment methods are undergoing trials, including pimavanserin, nilotinib, psychological interventions, and behavior therapy.

1. Introduction

Diffuse Lewy body disease (DLBD), or dementia with Lewy bodies (DLB), is the second most common cause of dementia, following Alzheimer's disease (AD) [1]. DLB accounts for 9.7% of people with dementia in population-based studies, and nearly 24.7% of people with dementia in clinic-based studies [2].

Lewy bodies were discovered in the brainstem of a patient with Parkinson's disease (PD) in 1912 [3], and since then the distribution of Lewy bodies was also found in the cortex and autonomic nervous system. In 1980, the term "Lewy body disease" (LBD) was proposed, and was classified into three types according to the distribution of Lewy bodies [4]: type A (brainstem type), type B (transitional type), type C (diffuse type). In 1996, a cerebral type was added, in which Lewy bodies were present in the cerebral cortex but rarely in the brainstem [4]. The brainstem type is consistent with PD, while the cerebral type shows no Parkinsonian symptoms during the disease course. The diffuse type is called "diffuse Lewy body disease" (DLBD). Patients with this type have both cognitive symptoms and parkinsonism, while Lewy

bodies distribute among the brainstem, limbic cortices, and the iso-cortex. In the transitional type (also called limbic type), the Lewy bodies were found in the brainstem and the limbic cortices, and the spectrum of clinical features lies between brainstem type and diffuse type [5,6]. The term DLBD was proposed in 1984 [7], and is defined as "progressive dementia and Parkinson symptoms of presenile or senile, or sometimes of younger onset, and neuropathologically by numerous Lewy bodies and neuronal cell loss in the central and autonomic nervous systems, frequently followed by various degrees of Alzheimer pathology" [8]. A recent study suggested the diffuse type had shorter disease duration compared with the transitional type, and this effect is independent of Braak stage [9].

Currently, LBD is a generic term including Parkinson's disease, Parkinson's disease with dementia (PDD), and DLB. In this article, we review the updated concept of DLB and the difference between DLB and PDD.

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Table 1
Diagnostic Criteria for Dementia with Lewy Bodies (DLB).

Criteria for the clinical diagnosis of DLB	
Essential clinical feature	Dementia progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities.
Core clinical features	Fluctuating cognition Recurrent visual hallucinations REM sleep behavior disorder Parkinsonism
Indicative biomarkers	SPECT or PET: Reduced dopamine transporter (DaT) uptake in basal ganglia. 123 Iodine-MIBG myocardial scintigraphy: Reduced uptake. Polysomnography (PSG): REM sleep without atonia.
Probable DLB:	
(1) Essential feature + 2 or more Core features ± indicative biomarkers; or	
(2) Essential feature + 1 Core feature + 1 or more indicative biomarkers.	
Possible DLB:	
(1) Essential feature + 1 Core feature	
(2) Essential feature + 1 or more indicative biomarkers.	

2. Clinical features and diagnostic criteria

The symptoms of DLB range from cognitive and mental disorders to motor and autonomic systems. Among the variety of clinical presentations, dementia, visual hallucinations, fluctuations in cognition, parkinsonism, and REM sleep behavior disorder (RBD) are the characteristic symptoms of DLB (Table 1).

According to the report of the DLB consortium, progressive

cognitive decline is essential for the diagnosis of DLB [10,11]. The cognitive profile of DLB shows more prominent attentional deficits and executive and visuospatial dysfunction compared to other types of dementia [12]. In the prodromal stage of DLB, a study shows lower performance on tests of executive function, visuoconstruction, and memory (free recall and visual recognition), as well as social cognition deficits and weakened visuospatial and praxic abilities, indicating the early involvement of high cortical function in patients with DLB [13]. The core features for diagnosing DLB are fluctuation in mental state, visual hallucination, parkinsonism, and REM sleep behavior disorder [10,11].

Cognitive fluctuations are defined as spontaneous alterations in cognition, attention, and arousal. In a study of brain magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI), DLB patients with fluctuations showed bilateral damage within thalamic regions projecting to the prefrontal and parieto-occipital cortices, suggesting microstructural thalamic damage and cholinergic imbalance may be the etiology of cognitive fluctuation [14]. There are several assessment scales for evaluating fluctuation, but the inter-rater reliability is inconsistent and accurate assessment is still difficult clinically.

Visual hallucinations are false perceptions that arise independently of actual visual scenes; they appear in over 70% of patients diagnosed clinically with DLB [15]. Visual hallucinations can be assessed using the Neuropsychiatric Inventory (NPI) hallucination score. This symptom correlates with cortical Lewy body burden and cholinergic degeneration in the neocortex. In a study of positron emission tomography with fludeoxyglucose (FDG-PET) on patients with DLB who had visual hallucinations, the uptake was reduced bilaterally in the medial occipital region. Reduced occipital metabolism seen in DLB is associated with the frequency and severity of visual hallucinations [16].

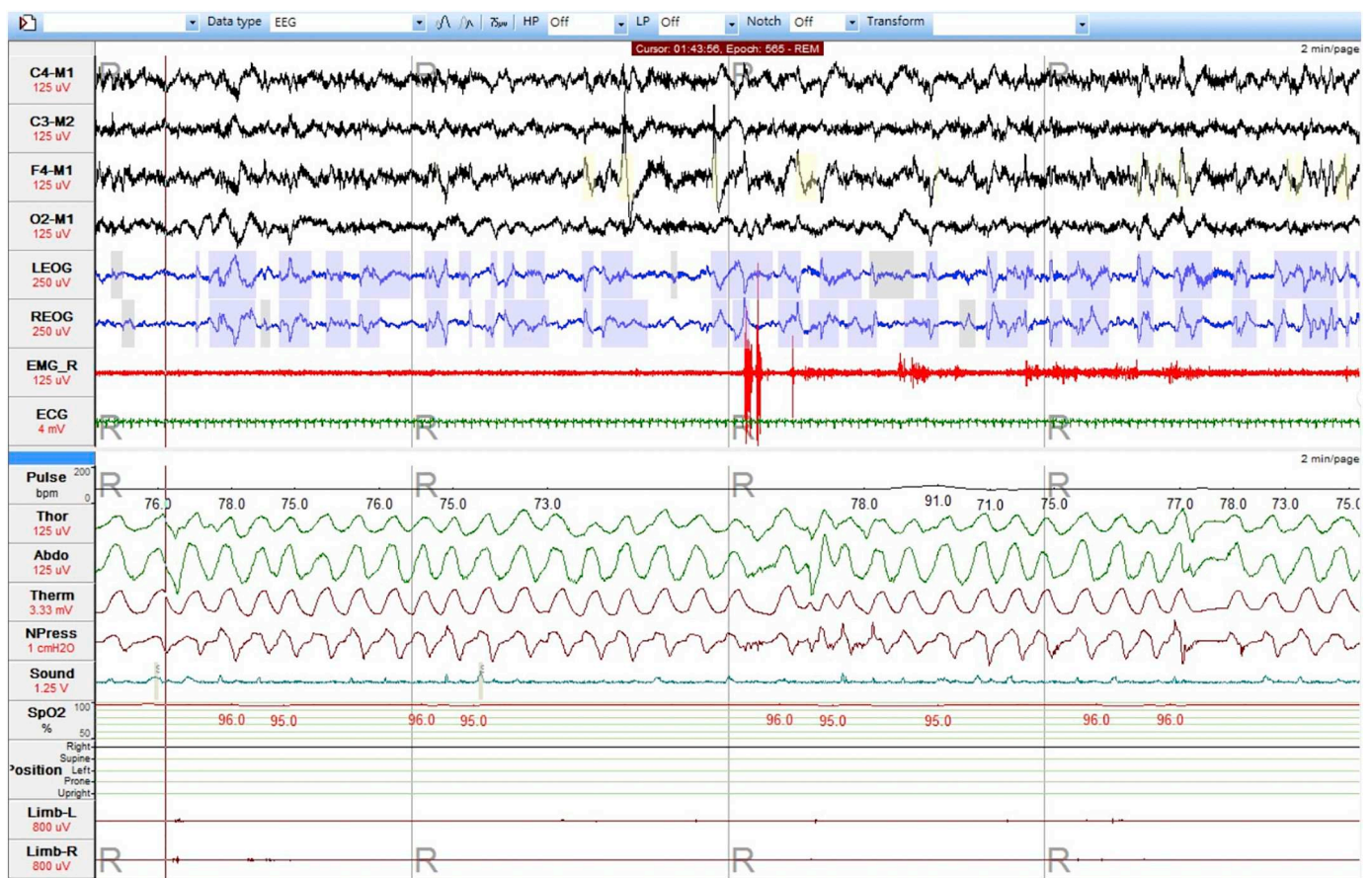


Fig. 1. Polysomnography of a patient with REM sleep behavior disorder. There was muscle activity during the REM sleep stage, demonstrating REM sleep without atonia (RSWA). Source: Dr. Chen-Hsien Huang, Sleep Center, YangMing branch, Taipei City Hospital, Taiwan.

The extrapyramidal motor symptoms of patients with DLB tend to involve axial movement, with greater postural instability and gait disorder (PIGD) compared to PD patients [8], and the response to levodopa is also less than in uncomplicated PD [17]. The severity of motor symptoms can be measured using the Unified Parkinson's Disease Rating Scale (UPDRS), but the evaluation may be complicated by the presence of cognitive dysfunction. In a study of dopamine transporter (DaT) scans, DLB patients with parkinsonism had significantly lower uptake in the entire striatum and putamen compared to DLB patients without parkinsonism [18].

REM sleep behavior disorder (RBD) is marked by symptoms of abnormal dream enactment, including usually violent words and movements during REM sleep. The disorder is diagnosed by polysomnography (Fig. 1), which shows REM sleep without atonia [19]. RBD is strongly associated with synucleinopathies such as PD, DLB, and multiple system atrophy (MSA) [20].

According to a study of patients with DLB, individuals with REM sleep behavior disorder were predominantly male and had a shorter duration of dementia, earlier onset of parkinsonism, and earlier onset of visual hallucinations [21]. These patients also had a lower Braak neurofibrillary tangle stage and neuritic plaque scores, but no difference in Lewy body distribution.

In addition to essential and core features, symptoms suggestive of a DLB diagnosis include severe neuroleptic sensitivity, autonomic dysfunction, depression, delusion, repeated falls, and syncope, but these are not specific for the diagnosis of DLB [10,11].

3. Pathology

According to the DLB consortium, the only neuropathologic requirement for diagnosing DLB is the presence of Lewy bodies in the brain of a patient with dementia [10]. In the fourth consensus report of the DLB consortium, Lewy-related pathology involving diffuse neocortical or limbic areas has higher likelihood of DLB diagnosis, compared to Lewy-related pathology in other CNS regions [11].

The main component of Lewy bodies is misfolded α -synuclein, a 140 amino acid protein encoded by the *SNCA* gene. This protein is richly represented in nuclei and presynaptic areas, and is found in many regions, including the substantia nigra, locus ceruleus, hypothalamus, nucleus basalis, cranial nerve motor nuclei, and the central and peripheral divisions of the autonomic nervous system [22,23]. Lewy bodies are also seen in the neurons of the cerebral cortex, particularly in the deep layers (V and VI) of the limbic system [24,25]. Current hypothesis postulates that Lewy pathology begins in the brainstem and is propagated upward to the cerebral cortex in PD [26]. In the cerebral type of LBD, Lewy pathology occurs in the cerebral cortex and propagates downward to the brainstem. Lewy pathology may also start from the olfactory bulb [27], while experimental findings showed that misfolded α -synuclein can transfer between cells and, once transferred into a new cell, can act as a seed that recruits endogenous α -synuclein, leading to formation of larger aggregates, similar to what has been shown in prion disease [28].

The Lewy pathology causes interruption of acetylcholine pathways, which may be related to cognitive dysfunction in DLB and PDD [29]. Visual hallucination in DLB is associated with Lewy bodies count in the posterior temporal region [30].

A recent study reveals that α -synuclein in various conformations can activate microglia.

Microglial activation is seen in vivo in Lewy body dementia. Pathological and biomarker studies provide further evidence of inflammation. Future studies need to link microglia with symptoms and structural change [31].

4. Genetics

SNCA, the gene encoding α -synuclein, was found to be mutated in

familial PD and DLB. These patients have point or copy number mutations in *SNCA* that are associated with hereditary, autosomal dominant forms of PD, DLBD, or neurodegenerative disease with parkinsonism [32].

There are six dominantly inherited missense mutations in *SNCA* linked to familial parkinsonism: A53T, A30P, E46K, H50Q, G51D, and A53E. Among these mutations, individuals with the A53T mutation in *SNCA* developed a severe form of PD that was accompanied by dementia [33]. A Spanish family with clinical features resembling DLB was found to have E46K mutation. The family members had autosomal dominant parkinsonism, dementia, and visual hallucinations of variable severity [34].

A next-generation sequencing study in North America found that mutation in *GBA* (glucocerebrosidase), *PSEN1*, and *APP* are common in patients with DLB [35]. A genome-wide association study revealed that DLB patients carried higher-risk variants or mutations in *APOE*, *GBA*, and *CTN-1* [36]. In a study of Ashkenazi Jews with DLB, mutations in the *GBA* gene were associated with more severe motor and cognitive dysfunction [37]. To date, only three genes have been convincingly established to be involved in DLB: *APOE*, *GBA* and *SNCA* [38].

5. Diagnostic tools

In addition to clinical criteria, several diagnostic tools are used to help physicians confirm the diagnosis and discriminate DLB from other types of dementia, such as dopamine transporter imaging (123I-FP-CIT single photon emission computed tomography [SPECT] or dopamine transporter [DAT] scan) and iodine meta-iodobenzylguanidine (MIBG) myocardial scintigraphy (Table 1).

Reduced DAT uptake in basal ganglia is one of the indicative biomarkers of DLB [9]. DAT imaging reveals the integrity of the nigrostriatal dopaminergic system and provides a marker for presynaptic neuronal degeneration [39]. Low striatal DAT activity appears in DLB, but not AD patients. When parkinsonism is the only core clinical feature in patients with dementia, reduced DA uptake warrants a probable DLB diagnosis [11]. 123I-FP-CIT SPECT plays a role in detecting the prodromal stage of DLB; during this stage, symptoms of long-term olfactory dysfunction or REM sleep behavior disorder may indicate more severe degeneration of the nigro-striatal dopaminergic pathway [40].

MIBG myocardial scintigraphy quantifies postganglionic sympathetic cardiac innervation. Cardiac MIBG uptake on 123I-MIBG cardiac scintigraphy is reduced in patients with Lewy body disease. It has been reported to be useful for differentiating DLB from AD, and detecting early-phase DLB, even before core clinical features appear [41]. Post-mortem studies have shown that the number of cardiac tyrosine hydroxylase (TH)-immunoreactive nerve fibers was decreased in Lewy body disease, supporting the findings of reduced cardiac MIBG uptake in Lewy body diseases [42]. Reduced uptake on MIBG myocardial scintigraphy is one of the indicative biomarkers of DLB [11,43].

A newly added indicative biomarker in the fourth consensus statement of the DLB consortium is polysomnography (PSG) confirmation of REM sleep behavior disorder [9]. According to ICSD-3, PSG recording demonstrating REM sleep without atonia (RSWA) is the diagnostic criterion for RBD (Fig. 1). In a study of polysomnography on DLB patients with sleep-related complaints, several sleep disturbances in addition to REM sleep behavior disorder are frequently present [37]. About three-quarters of patients had a significant number of arousals that were not accounted for by a movement or breathing disturbance [44].

Other supportive biomarkers include findings on SPECT and electroencephalography (EEG) studies. In a study by the Alzheimer's Disease Neuroimaging Initiative (ADNI), occipital FDG-PET hypometabolism accurately classified coincident DLB in dementia patients [45]. Posterior slow-wave activity with periodic fluctuation of pre-alpha/theta activities on EEG is also characteristic in patients with DLB [46]. A multicenter study of quantitative EEG also showed specific

abnormalities in posterior deviations in DLB patients that can be discriminated from AD [47].

There are no definite cerebrospinal fluid (CSF) biomarkers for DLB, but a large multicenter cohort study revealed that a large increase in abnormal value of A β 42 combined with abnormal increase in t-tau and/or p-tau in CSF was more common in DLB than with PDD and PD; the abnormal CSF finding was also associated with more severe cognitive impairment in DLB [48].

6. Differences between DLB and PDD

According to the criteria of the DLB consortium, DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism (if it is present), and the term PDD should be used to describe dementia that occurs in the context of well-established Parkinson's disease [10].

Longitudinal cohort studies demonstrate that the prevalence of dementia in Parkinson's disease (PDD) is about 30%, and at least 75% of PD patients who survive for > 10 years will develop dementia [49]. Neuropsychiatric symptoms in PDD were more like those in AD than in DLB, while severe neuropsychiatric symptoms in degenerative dementia were associated with DLB [50]. Visual hallucination tends to appear in the early years of DLB, but this symptom usually appears in late-stage PDD.

Although both DLB and PDD patients have deficits in processing speed as well as executive and visuospatial function in the neuropsychological profiles, in the early stage of dementia, DLB patients have worse performance on tests of attention, executive functions, and constructive abilities compared to PDD patients [51], and also have more rapid decline of cognitive function [52]. In contrast, at the mild dementia stage, motor symptoms are more advanced in PDD than in DLB [50].

The motor subtype of PDD is similar to DLB, with more common postural instability gait difficulty (PIGD) features than tremor dominant (TD) features. In addition, a study showed a PIGD motor subtype is associated with a faster rate of cognitive decline in PD and may be considered a risk factor for incident dementia in PD [53]. However, L-dopa replacement is less effective in DLB than for PD [17].

Lewy bodies are the core pathology findings in both DLB and PDD. Some studies showed Lewy bodies almost always involving the limbic system in patients with DLB, and α -synuclein involvement in the striatum may be greater in DLB, while neuronal loss in the substantia nigra was reported to be greater in PDD patients [54,55]. β -amyloid pathology is more common in DLB patients, which can be a potential biomarker for distinguishing between DLB and PDD [56].

In a study of functional MR voxel-based morphometry (VBM) analysis, PDD showed significant bilateral frontal atrophy, whereas DLB was characterized by predominant parietal and occipital atrophy; a similar involvement of subcortical regions in PDD and DLB was observed [57].

Because PDD shares many underlying clinical and pathological features with DLB, the 1-year rule distinguishing between DLB and PDD may be difficult to apply in clinical settings; both clinical phenotypes may be considered collectively under categories such as LB disease or α -synucleinopathy [10]. The current concepts of differences between DLB and PDD are summarized in Table 2.

7. Management

According to the guideline of the British Association for Psychopharmacology, cholinesterase inhibitors should be used for the treatment of people with Lewy body dementias (both PDD and DLB), and memantine also may be helpful [58]. Randomized controlled trials of cholinesterase inhibitors vs placebo demonstrated modest but significant benefits in cognition, behavioral symptoms, and global functions. Visual hallucinations are associated with greater deficits in

cortical acetylcholine and also respond to cholinergic therapy [59].

Dopamine agonists have a greater tendency to induce compulsive behavior, hallucinations, and somnolence; therefore, levodopa is a better choice for managing parkinsonism in DLB. However, there is only a partial response of motor symptoms to levodopa in DLB patients [17,60].

Preventing falls is very important for DLB patients, and physical therapy and home modification may improve motor symptoms and prevent falls [61]. Anticholinergics should be avoided because they may exacerbate cognitive dysfunction.

For REM sleep behavior disorder and other sleep disturbances in DLB patients, low-dose clonazepam, melatonin, or quetiapine may help [10]. The first-line drug for sleep disturbances is melatonin, and the second-line drug is clonazepam. Melatonin can restore the atonia in REM sleep, while clonazepam blocks the locomotor generation directly. An animal study showed that melatonin has a neuroprotective effect on Parkinson's disease, but the effect on DLB hasn't been confirmed [62].

Autonomic symptoms in DLB patients include orthostatic hypotension, gastroparesis or constipation, urinary dysfunction, and sexual dysfunction. In addition to medications for symptom control, discontinuation of causative drugs, patient education, and physical training help eliminate disability and improve quality of life [63].

According to consensus guidelines for the treatment of orthostatic hypotension, correction of aggravating factors and nonpharmacological treatment such as increasing salt and fluid intake, physical activity and compression stockings should be applied before pharmacological management [64,65]. For patients with symptomatic orthostatic hypotension, fludrocortisone can help patients with volume depletion, and midodrine is used for patients without hypovolemia. Both medications may cause supine hypertension and should be used with caution [64].

As to gastroparesis and constipation, dietary modifications are essential for gastric motility and nutrition supply [65]. Available medications for gastroparesis include D2-receptor blockers or motilin receptor blockers. For constipation, psyllium and polyethylene glycol showed efficacy in increasing bowel movement frequency [66,67].

Neurogenic detrusor overactivity is a common problem in DLB, and usually presents as urinary frequency, urgency, and incontinence [68]. Trospium is a peripherally acting antimuscarinic with low CNS penetration and improves symptoms of detrusor overactivity [63,65]. Anticholinergics or antimuscarinic agents with CNS penetration should be avoided because of the adverse effect of cognitive impairment.

For patients with sexual dysfunction, sildenafil improved erectile dysfunction in a small randomized trial of patients with synucleinopathies [69].

Because of severe neuroleptic sensitivity in approximately 50% of DLB patients [10], antipsychotic agents are not well tolerated by DLB patients. Pimavanserin, a selective serotonin 5-HT_{2A} inverse agonist, has been approved to treat psychosis in PD patients; it is now undergoing trial for improving hallucinations and delusion in DLB patients [70].

Other Phase I clinical studies conducted for the treatment of DLB include nilotinib [71] and deep brain stimulation (DBS) targeting the nucleus basalis of Meynert (NBM) [72].

Nilotinib is an abl tyrosine kinase inhibitor and has the potential to decrease α -synuclein degradation [71]. DBS targeting NBM in PDD patients showed improvement in cognitive function [72], but the evidence supporting efficacy of DBS on DLB patients is weak.

Because of emotional fluctuations and behavioral disorders, DLB patients cause greater social costs and caregiver burden than AD patients. Medication therapy for DLB is also challenging because treating one symptom can produce other complications. Individualized counseling, training of caregivers, and nonpharmacological interventions that increase social interaction, remove triggers, and offer comfort can be effective in addition to pharmacotherapy, both for cognitive and noncognitive symptoms [58,73]. Table 3 summarizes the current

Table 2
Differences between Dementia with Lewy Bodies (DLB) and Parkinson's Disease with Dementia (PDD).

	DLB	PDD
Diagnosis criteria	Dementia appears before or concurrently with Parkinsonism	Dementia appears > 1 year after Parkinson is diagnosed
Signs	Cognition decline predominates	Motor decline predominates
Early stage	A. Attentional and conceptual errors	Deficits in processing speed, executive and visuospatial function in early dementia stage
Cognition	B. Deficits in processing speed and executive function	Hallucinations appear in later stages
Neuropsychiatric symptoms	A. Early hallucinations and psychoses B. More adverse reaction to anti-psychotic agents	
Motor symptoms and signs	A. Less tremor B. Postural instability and gait disorder (PIGD) predominates C. Less response to L-dopa	PIGD also predominates but asymmetric features are more likely
Pathology	A. More neuronal loss in striatum B. Greater beta-amyloid level than PDD	More neuronal loss in the substantia nigra
Imaging study	Parietal-occipital atrophy	Bilateral frontal atrophy

Table 3
Management of dementia with Lewy bodies.

Symptoms & Signs	Management
Dementia	Cholinesterase inhibitors
Neuropsychiatric symptoms	A. Cholinesterase inhibitors B. Psychological intervention C. Pimavanserin (under trial)
Parkinsonism	Levodopa
REM sleep behavior disorder	A. First line: melatonin B. Second line: clonazepam
Autonomic dysfunction	A. Fluid intake, exercise, compression stockings B. Fludrocortisone C. Pressor agents: midodrine, droxidopa
Orthostatic hypotension	A. Dietary modifications B. Gastroparesis: D2 receptor blockers/motilin receptor blockers C. Constipation: psyllium
Gastroparesis/Constipation	Tropium
Detrusor Overactivity	Sildenafil
Sexual dysfunction	

consensus regarding management of DLB patients.

The most common cause of death in patients with dementia was pneumonia, followed by cardiovascular disease and sepsis [74]. Community-dwelling demented patients had more comorbid conditions, such as cardiovascular and lung disease and urinary tract infections, compared to controls without dementia. According to a study, 69.8% showed evidence of cardiovascular disease, including old or recent MI; 20.9% had lung disease; and 18.6% had urinary tract infections [74]. Understanding the causes of death and associated comorbidities in individuals with various subtypes of dementia is important in assessing end-of-life care for these individuals.

8. Conclusions

The revised criteria of the DLB consortium help clinicians make diagnosis more precisely, and let physicians pay more attention to this dementia subtype.

As the second most common cause of dementia, DLB is a challenge not only to patients, but also physicians and caregivers. We need all-directional and multidisciplinary strategies to alleviate the social and economic burdens.

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