Parkinson's Disease Dementia versus Dementia with Lewy Bodies

Catherine Agbokou, MD, MSc, *Service de Psychiatrie Adulte, Hôpital Pitié-Salpêtrière, Université Pierre et Marie Curie, Paris, France.*

Emmanuel Cognat, MD, *Service de Psychiatrie et de Psychologie Médicale, Hôpital Saint-Antoine, Université Pierre et Marie Curie, Paris, France.*

Florian Ferreri, MD, MSc, *Service de Psychiatrie et de Psychologie Médicale, Hôpital Saint-Antoine, Université Pierre et Marie Curie, Paris, France.*

Differentiating between Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) is a difficult issue for many clinicians. To date, these diseases share most of their clinical, neuropathological, and management features. Therefore, PDD and DLB are considered by some authors to be the two extremities of a single spectrum disease named Lewy body diseases. Nevertheless, specific diagnostic criteria now exist for each disease and specific diagnosis remains of interest in clinical practice. In this article, we summarize features and diagnostic criteria of both PDD and DLB, compare them, and examine their treatment options.

Key words: *Parkinson's disease dementia, dementia with Lewy bodies, Lewy body disease, movement disorders, dementia, treatment*

Introduction

Parkinsonism is a neurological syndrome characterized by three main symptoms: hypokinesia (slow or diminished movement of body not linked to muscle strength decrement or apraxia); extrapyramidal "lead-pipe" rigidity; and rest tremor. Several diseases may present with parkinsonism and cognitive disturbances (Table 1). Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) are the most frequent, and currently differentiating between them can be especially difficult. Even though some authors have proposed that DLB and PDD are the two extremities of the single spectrum of Lewy body disease (LBD), to date these conditions remain considered two different entities with specific diagnostic criteria. However, because of the clinical and neuropathological overlap between the two illnesses, distinguishing between DLB and PDD can be difficult in clinical settings. In this article, we report the main features of both diseases, underline the clinical differentiation between them, and summarize the main considerations of management.

Parkinson's Disease Dementia

Parkinson's disease has been primarily considered a motor disorder. Currently, cognitive disorders in Parkinson's disease are increasingly recognized, partly because of the longer life expectancy provided by recent therapeutic advances. Estimates of the overall prevalence of dementia among patients with Parkinson's disease vary, but a figure of about 30% is generally accepted. The mean duration of Parkinson's disease before dementia occurs is about 10 years, but wide variations may be observed.[1] Identified risk factors for PDD include older age, akinetic-rigid form, and early hallucinations.[1,2] The main impaired cognitive functions in PDD are attention, executive, and visuospatial functions.[1] Memory may also be impaired, but it is not a mandatory feature and, when disturbed, the degree of impairment is usually less than that seen in Alzheimer's disease.[1,3]

Diagnostic Criteria

In 2007, the Movement Disorders Society Task Force proposed formalized diagnostic criteria for PDD.[3] These criteria are separated in two levels. The first level requires no special neuropsychological skills to use and is thus usable by any clinician. The second level is more descriptive and is suitable for use in research and longitudinal follow-up. Diagnosis of PDD at level 1 requires that the patient fulfill five criteria (Table 2). First, a diagnosis of Parkinson's disease must have been made according to the Queen Square Brain Bank criteria (except for the lack of dementia). Second, Parkinson's disease must have developed prior to dementia. Third, cognitive deficiency must be severe enough to impair activities of daily living. As an alternative to a caregiver interview, the authors propose using the Pill Questionnaire, which assesses the patient's knowledge about drugs, doses, and timing of treatment. Fourth, global cognitive efficiency must be decreased: a cutoff score of <26 out of 30 on the Mini-Mental State Examination (MMSE) has been proposed. Finally, the profile of cognitive deficits must be typical of those described in PDD—that is to say, alterations in two or more of four domains: (1) attention, assessed by asking the patient to repeatedly subtract seven starting at 100 (serial sevens of the MMSE) or to state the months of year backwards (months reversed); (2) executive

Table 1: Causes of Parkinsonism Associated with Dementia among Older Adults

Condition	Main Additional Features
Alzheimer's disease	Gradual development of forgetfulness Associated aphasia, apraxia, and/or agnosia
Cerebrovascular disease	History of stroke or transient ischemic attack Subcortical white matter changes on brain imaging
Corticobasal degeneration	Limb apraxia Usually late mental deterioration
Creutzfeldt-Jakob disease	Confusion, hallucinations, other visual disturbances Cerebellar ataxia Myoclonic jerks
Frontotemporal dementia	Prominent behavioural disturbances: usually apathy, sometimes euphoria
Human immunodeficiency virus (HIV) dementia	HIV infection Abnormalities in motor functions White matter changes on brain magnetic resonance imaging
Huntington's disease	Subcortical dementia Psychiatric features (irritability, impulsiveness, disorders of mood) Chorea
Multiple system atrophy	Cerebellar ataxia Orthostatic hypotension and other features of autonomic nervous system involvement
Normal pressure hydrocephalus	Gait disturbances Frontal lobe dysfunction Urinary incontinence
Progressive supranuclear palsy	Supranuclear ophthalmoplegia (vertical direction of gaze) Unsteadiness of gait and repeated unexplained falling

Sources: Adapted from Camicioli R et al., Fisher N, 2004,[13] and Ropper AH et al., 2005.[17]

functions, assessed by using the lexical verbal fluency test (to evoke in a limited amount of time the maximum number of words that begin with the same letter) or the clock-drawing test (to draw a clock with the hands showing "10 past 2"); (3) visuoconstructive ability, judged on the drawing of MMSE pentagons; and (4) memory, assessed using the three-word recall of MMSE.

Dementia with Lewy Bodies

Dementia with Lewy bodies is now considered to be the second most common dementia subgroup, after Alzheimer's disease.[4] Dementia with Lewy bodies corresponds to a clinical pattern of cognitive and non cognitive signs usually associated with Lewy body pathology at autopsy (up to 90% with current diagnostic criteria[5]). This unifying term[4] has replaced several older diagnostic appellations, such as Lewy body variant of Alzheimer's disease, Lewy body dementia, senile dementia of Lewy body type, and cortical Lewy body disease. The mean age at onset is 75 years.[6] Typical features are progressive cognitive decline associated with parkinsonism (often with an akinetic-rigid presentation and prominent axial involvement); severe fluctuations in vigilance, attention, and cognitive performances; and/or early spontaneous visual hallucinations. Atypical presentations are not rare. Other key features include severe sensitivity to neuroleptic agents and rapid eye movement (REM) sleep behaviour disorder, in which a loss of muscle atonia is associated with REM sleep, and "acting out" dreams. Disease progression is usually faster than that in Alzheimer's disease (four to five points decline per year on the MMSE) with a survival of <10 years.[7]

Diagnostic Criteria

Consensus guidelines for DLB diagnosis were first published in 1996. An international workshop on dementia with Lewy bodies has twice revised these guidelines. The most current version was published in 2005.[5] The article includes clinical diagnostic criteria divided into central (mandatory for diagnosis), core (two core

Table 2: Diagnostic Criteria for Parkinson's Disease Dementia*

Diagnosis of Parkinson's disease based on the Queen Square Brain Bank specific criteria
Impact of cognitive deficits on daily living
MMSE score <26/30
Parkinson's disease developed prior to the onset of dementia
Impairment in two of the following cognitive functions: • Attention (months reversed or serial 7s of MMSE) • Executive functions (lexical fluency or clock-drawing test) • Visuospatial abilities (MMSE pentagons) • Memory (MMSE 3-word recall)

MMSE = Mini-Mental State Examination; PDD = Parkinson's disease dementia
*Every criterion has to be fulfilled to support the diagnosis of probable PDD.
Presence of other disease that could explain part or all of clinical picture (including delirium and depression) makes the diagnosis uncertain

Source: Adapted from Dubois B et al., 2007.[3]

features are sufficient for diagnosis of probable DLB, one for possible DLB), suggestive (if one or more is present in the absence of any core feature, a diagnosis of possible DLB may be made; if associated with one core feature, a diagnosis of probable DLB may be made), and supportive (commonly found among individuals with DLB but without proven diagnostic specificity) features (Table 3).

Table 3: Diagnostic Criteria for Dementia with Lewy Bodies*

Central feature: Dementia, which must occur before or within 1 year of parkinsonism onset ("rule of 1 year")
Core features: Fluctuations in cognitive performances, recurrent visual hallucinations, spontaneous features of parkinsonism
Suggestive features: REM sleep behaviour disorders, severe sensitivity to neuroleptic drugs, low dopamine transporter uptake in basal ganglia on SPECT or PET imaging
Supportive features (have no diagnostic specificity and can only reinforce a diagnostic of possible or probable DLB based on core and suggestive features): repeated falls and syncope; transient, unexplained loss of consciousness; autonomic dysfunction; systematized delusions; depression; relative preservation of medial temporal lobe structures on brain imaging; generalized low uptake on SPECT or PET scan with reduced temporal lobe activity; low uptake of MIBG on myocardial scintigraphy; and prominent slow wave activity on electroencephalography with temporal lobe transient sharp waves
Elimination of other illness that might explain part or all of clinical picture

DLB = dementia with Lewy bodies; MIBG = meta-iodobenzylguanidine; PET = positron emission tomography; REM = rapid eye movement; SPECT = single-photon emission computed tomography
*Diagnosis of probable DLB: the presence of the central feature plus 2 core features or 1 core feature plus at least 1 suggestive feature; diagnosis of possible DLB: the presence of the central feature plus 1 core feature or any number of suggestive features without any core feature.

Source: Adapted from McKeith IG et al., 2005.[5]

In addition, dementia should occur prior to or at the same time as parkinsonism (at a maximum of 1 year after dementia onset according to the "rule of 1 year"), and other illnesses that may account for the symptoms or suggestive features of such diseases must be ruled out. The central criterion corresponds to the dementia itself, that is, a progressive decline in cognitive functions sufficient to impair activities of daily living. The core features are the presence of cognitive fluctuations, particularly in attention and alertness; recurrent visual hallucinations; and spontaneous features of parkinsonism (in the absence of any other cause, particularly iatrogenic [e.g., drug] causes). Suggestive features include REM sleep behaviour disorder, severe sensitivity to neuroleptics, and low dopamine transporter uptake in the basal ganglia seen on brain imaging with positron emission tomography or single-photon emission computed tomography.

Parkinson's Disease Dementia and Dementia with Lewy Bodies: Similarities and Differences

Whether PDD and DLB are distinct entities or the two ends of a single disease spectrum is an issue that remains undetermined. However, some key information is worth emphasizing to shed some light on how to deal confidently with PDD and DLB in everyday practice. PDD and DLB share a single neuropathological abnormality: Lewy bodies. Lewy body disease is now an accepted diagnosis in uncertain cases (particularly when time sequence is confusing) according to the third revision of DLB clinical criteria; this has the advantage of including very diffuse clinical manifestations under a single descriptive term.[5]

Except for the age of onset, temporal course, and levodopa responsiveness, no major differences between PDD and DLB have been found in terms of cognitive, autonomic, and neuropsychiatric features or response to treatment (Table 4).[8] Management issues are usually the same. Thus, McKeith recently wondered if the distinction between the two diseases is of

any practical significance. But for patients, families, and caregivers, it seems that receiving one diagnosis or the other is of importance as it underlines the main problem they will have to face. The distinction seems less important to the scientific and research communities, which focus on the pathological process and treatment issues.[9] An easy way to distinguish between DLB and PDD is to use the rule of 1 year. This arbitrary rule states that DLB may be diagnosed only when cognitive disturbances precede parkinsonism or when dementia appears <1 year after the onset of parkinsonism. If not, a diagnosis of PDD or another form of dementia must be considered.[5]

Management

As in other dementias, physiotherapy, nursing, social support, and counselling of patients, family, and caregivers are of particular benefit. Regarding pharmacotherapy, evidence to guide the clinical management of PDD and DLB is limited.[10] However, some recommendations may be drawn based on existing trials and everyday practice (Table 5).

Although levodopa therapy has been described as less effective in PDD and DLB than in Parkinson's disease, to date the treatment of motor features of PDD and DLB is based on this therapy.[5,11,12] The adjustment of dopa therapy is difficult since optimizing motor function with increasing doses of dopaminergic drugs typically precipitates psychosis. Thus, clinicians must use dopaminergic medications at the lowest efficient dose.

With respect to cognitive features, cholinesterase inhibitors may be helpful in improving cognitive functions and reducing neuropsychiatric symptoms.[13] Two double-blinded studies using rivastigmine (6–12 mg/d) showed significant benefit, with a particular improvement in attention.[14,15] Side effects were principally nausea, vomiting, and worsening tremor in about 10% of patients.[12] In PDD and DLB, anticholinergic drugs (e.g., those used in urinary incontinence or tricyclic antidepressants) should be avoided. Also, exacerbating factors of cognitive impairment (metabolic factors, dehydration, infections) should be eliminated.

Regarding hallucinations, the first step in management is to optimize dopaminergic therapy. Cholinesterase inhibitors also have proven benefits.[11] Finally, specific treatment is often needed. Classic neuroleptic drugs may lead to severe adverse reactions in both PDD and DLB and should not be used.

Table 4: Comparison of Main Features of Parkinson's Disease Dementia and Dementia with Lewy Bodies

Feature	Parkinson's Disease Dementia	Dementia with Lewy Bodies
Parkinsonism	100%	~75%
Tremor	++	+/–
Axial motor symptoms	++	+++
Hallucinations and other psychiatric symptoms	++	+++
Delay between parkinsonism onset and dementia	Several years	Maximum 1 year
Sensitivity to neuroleptics	++	+++
Levodopa responsiveness	+++	+

Source: Adapted from Emre M et al., 2007[1]; McKeith IG et al., 2005[5]; McKeith I, 2007[9]; and Lippa CF et al., 2007.[12]

Table 5: Main Management Options for Parkinson's Disease Dementia and Dementia with Lewy Bodies

	Treatment
General measures	Avoidance of any potential iatrogenic medication Counselling Physiotherapy
Cognitive dysfunctions	Cholinesterase inhibitors (rivastigmine 6–12 mg/d)
Visual hallucinations	Levodopa therapy adjustment Low doses of atypical antipsychotics (clozapine 12.5–50 mg/d, quetiapine 50 mg/d) Cholinesterase inhibitors (rivastigmine 6–12 mg/d)
Parkinsonism	Levodopa (lowest efficient dose)
Rapid eye movement sleep behaviour disorder	Clonazepam (0.5 mg h.s.)
Depression	Selective serotonin reuptake inhibitor, serotonin-norepinephrine reuptake inhibitor

Source: Adapted from Poewe W, 2005.[11]

Key Points

Parkinson's disease dementia and dementia with Lewy bodies are frequent causes of dementia associated with parkinsonism and share many of their clinical and neuropathological features.

Specific diagnostic criteria now exist for both diseases. The time sequence remains the most important criteria for distinction between PDD and DLB.

Lewy body disease is an accepted diagnosis in uncertain cases.

The main treatment options consist in levodopa therapy (for motor features), cholinesterase inhibitors (for cognitive disturbances), atypical antipsychotics (for hallucinations) and avoidance of treatments adverse effects.

Among atypical antipsychotics, only clozapine has proven safety and efficacy in controlled studies (in Parkinson's disease), but the use of this drug remains limited by severe hematological adverse effects and restricting blood monitoring.[11] Quetiapine, a molecule close to clozapine, has been suggested by small open studies and a meta-analysis to be efficient and safe to use in patients with PDD or DLB,[16] but scientific evidence from controlled studies is lacking.

Finally, patients with PDD or DLB are particularly at risk for treatment adverse effects. Therefore, any nonessential medications should be avoided or discontinued. For example, antihypertensive drugs may worsen orthostatic hypotension, one of the most disabling and dangerous dysautonomic features presented in patients with DLB or PDD.

Conclusion

Parkinson's disease dementia and DLB share many features in terms of clinical presentation, treatment options, and their underlying pathological process. However, specific diagnosis remains important, at least for patients and caregivers. To help practitioners in this matter, simple, sensitive, and specific diagnostic criteria now exist for both of these diseases. Some scientific evidence is still lacking for the treatment of several of their complications, but cholinesterase inhibitors and atypical neuroleptics such as clozapine are central tools for the management of PDD and DLB neuropsychiatric features. ga

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