
The Emerging Spectrum of Parkinsonian Dementias

This is the first in a two-part article examining the emerging spectrum of parkinsonian dementias. The first part looks at pathology and neurochemistry, the clinical features and differences between dementia with Lewy bodies (DLB), the dementia of Parkinson's disease (PDD) and the advanced stages of Alzheimer's disease (AD). The second part of the article will appear in the next issue of the *Canadian Alzheimer Disease Review* and will examine the treatment of DLB, PDD and AD.

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There is increasing recognition of the group of dementias that are manifest with parkinsonism, behavioral symptoms and cognitive impairment. The clinical spectrum of such disorders includes: dementia with Lewy bodies (DLB), the dementia of Parkinson's disease (PDD) and the advanced stages of Alzheimer's disease (AD). Unifying this spectrum is an underlying mix of neuropathological lesions, including Lewy bodies, α -synuclein deposition and senile neuritic plaques.

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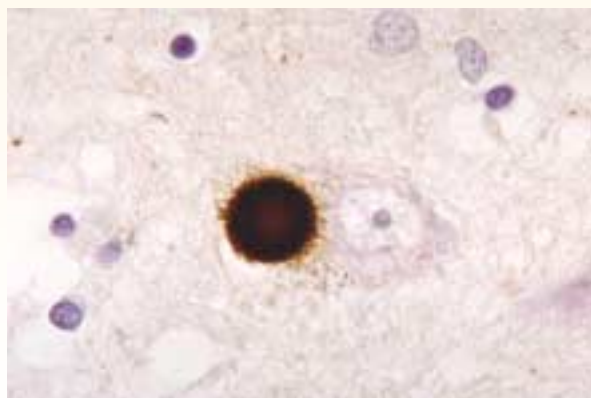
DLB is an increasingly recognized form of dementia. In a recent study of individuals referred to dementia centres in Canada, the ACCORD study, DLB accounted for 1.9% of the primary diagnoses of dementia while 2.7% of dementia diagnoses were mixed AD and DLB.¹ There is a suggestion from the neuropathologic literature that DLB may be the second most common cause of dementia, accounting for up to 25% of cases at autopsy.² The average age of onset of DLB is 67 years, with males more affected than females (62% vs. 38%).³ The average duration of illness is nine years,³ though estimates of speed of progression vary considerably from study to study.⁴ At the present time the neuropathological diagnosis is made more frequently than the clinical diagnosis. Further work is

required to enhance the clinical diagnosis of this condition.

PDD is also becoming more recognized. Estimates of the prevalence of dementia in patients with Parkinson's disease (PD) vary widely, but usually range from 20% to 45% depending on the definition of dementia used.⁵ In the ACCORD study,¹ PDD accounted for 0.6% of patients referred for dementia, but this estimate of its frequency was subject to a significant selection bias, as the ACCORD study was conducted in dementia research centres and not PD units. In one longitudinal study of the incidence of dementia in a community-based sample of patients with PD, the incidence of dementia was 95.3 per 1,000 patient years.⁶ When the risk of dementia in PD patients was compared to that of control subjects, the risk of devel-

Figure 1

The Lewy Body: Spherical, Eosinophilic Intracellular Inclusions Located Within Neurons



oping dementia was 5.9 times higher in the PD group (OR 5.9, 95% CI, 3.9-9.1). Risk factors that predict the development of dementia in PD include age, age of onset of PD, depression and more severe motoric parkinsonian symptoms.^{6,7,8}

In AD, extrapyramidal features typically occur in more advanced disease stages. In the Canadian study of Health and Aging, a population-based study of persons over 65 years of age, 9% of patients identified with AD had parkinsonism.⁹ The reported rate of parkinsonism in AD ranges from 12% to 92% depending on the study.¹⁰ Explanations for this wide variability in frequency have been linked to the definition of extrapyramidal features studied, inclusion of patients on neuroleptics, inclusion of patients with DLB in earlier studies, and the specific population of AD patients studied.^{10,11}

Extrapyramidal symptoms (EPS) become more common with disease progression,¹⁰ and are associated with increased mortality. This increased risk of mortality is independent of severity of cognitive impairment, age and residential status.⁹ EPS occurring in AD predicts a worse outcome.

Pathology and Neurochemistry

Pathological findings. The Lewy body (LB) is the pathologic hallmark of DLB. LBs are spherical, eosinophilic intracellular inclusions located within neurons (Figure 1). They are composed of neurofilaments, crystallin, ubiquitin, and α -synuclein, a protein that aggregates and which is important in a number of neurodegenerative diseases^{3,12} (Table 1). These diseases are all characterized by inclusions containing α -synuclein. With the exception of multi-system

atrophy and its subtypes, all of these disorders also have LBs as part of their neuropathology.

Initially described in brainstem nuclei as one of the pathologic markers of PD,² LBs occur throughout the brain in patients with DLB. They have a predilection for certain areas of the brain: brainstem, subcortical nuclei, limbic cortex (especially cingulate, entorhinal, and amygdala) and neocortex (temporal > frontal = parietal).¹³ LBs in DLB are more easily seen and better defined in the brainstem than the cortex, where they can be more easily missed if special staining methods are not used. They are best seen using antibodies to α -synuclein.¹²

AD pathology usually coexists with the typical pathology of DLB, though there rarely will be evidence of DLB pathology without evidence of β -amyloid plaques and neurofibrillary tangles. The burden of the AD pathology in DLB patients is less than was found in a cohort of "pure" AD patients with similar or worse disability prior to death.¹⁴

In PD, LBs are classically found in the ventrolateral portion of the substantia nigra, and are associated with cell loss. These changes result in the loss of nigrostriatal dopaminergic projection neurons, and they are thought to be responsible for the extrapyramidal movement disorder that is seen.⁵ To a lesser extent, the LBs can be

Table 1

The Synucleinopathies

- Lewy Body Diseases
 - Idiopathic Parkinson's disease
 - Dementia with Lewy Bodies
 - Incidental Lewy Body "disease"*
 - Rare sporadic syndromes associated with Lewy bodies
 - Pure Autonomic Failure
 - Lewy Body Dysphagia
 - Inherited Lewy body diseases
 - Mutations of the α -synuclein gene, PARK3 and PARK4

- Multiple System Atrophy
 - Olivopontocerebellar Atrophy
 - Striatonigral Degeneration
 - Shy-Drager Syndrome

* Incidental Lewy bodies found on brain autopsy but not associated with clinical disease.

found in other brainstem nuclei, and throughout the cerebral cortex. As in DLB, co-existent AD pathology is often seen in PDD, with β -amyloid plaques, and neurofibrillary tangles in excess of that expected in age-matched normal controls, at times in sufficient quantity to meet criteria for AD.¹⁵

The pathology of the parkinsonian changes in AD is less clear. In 20% to 85% of autopsy-confirmed cases of AD with associated clinical parkinsonism, nigral degeneration with LBs is found.¹⁰ This suggests a co-existent diagnosis of PD in at least some patients. Other patterns seen at autopsy include neurofibrillary tangles in the substantia nigra and cell loss without any pathological inclusions. Other

patients who have parkinsonism during life do not have any demonstrable nigral pathology. Pathologic mechanisms suggested for this group include pathology in other dopaminergic pathways (e.g., mesocortical), and increased β -amyloid plaque in the striatum.¹⁰

Neurochemical abnormalities.

There is significant neurotransmitter disruption in DLB. Neuropathologic studies have shown that there is a decrease in choline acetyltransferase (ChAT, the rate-limiting enzyme for the synthesis of acetylcholine) in DLB. This cholinergic marker deficit is even greater in DLB than in AD.^{16,17} The loss of ChAT activity is paralleled by a loss of neurons from the nucleus basalis of Meynert, the

primary source of cholinergic input to the cortex.¹⁷ Low mid-frontal neocortical ChAT levels correlate significantly with low scores on the mini mental status exam (MMSE).¹⁶

There is disruption of the dopaminergic system in DLB. The mesolimbic, mesocortical, and striatonigral pathways show evidence of degeneration, largely due to involvement of the ventral tegmental area and the substantia nigra.³ The disruption of the nigrostriatal pathway is responsible for the parkinsonian features seen in DLB.

The neurochemical abnormalities found in PDD are very similar to those found in DLB. There is disruption of cholinergic input to the cortex due to neuronal loss and LB formation in the nucleus basalis of Meynert. This loss is usually > 70% in patients with PDD and is significantly greater than in patients with PD without dementia.⁵ As in DLB, the loss of cholinergic activity is purported to account for much of the cognitive decline seen in PDD. The loss of the nigrostriatal tract is responsible for the extrapyramidal movement disorder, but also may play a role in some cognitive dysfunction, through its connections with fronto-caudate feedback loops.⁵

The cholinergic hypothesis of AD states that the cognitive deficit seen is primarily due to the loss of cholinergic input to the

Table 2

Consensus Criteria for the Clinical Diagnosis of Probable and Possible DLB

1) *Progressive cognitive decline, of sufficient magnitude to interfere with normal social or occupational function.*

- may or may not have prominent memory dysfunction at onset but usually evident with progression
- may have prominent deficits on tests of attention, frontal-subcortical skills, and visuospatial ability

2) *For Probable DLB 2 of (for Possible DLB 1 of):*

- fluctuating cognition with pronounced variations in attention and alertness
- recurrent visual hallucinations that are typically well formed and detailed
- spontaneous motor features of parkinsonism

3) *Features supportive of the diagnosis are:*

- repeated falls
- syncope
- transient loss of consciousness
- neuroleptic sensitivity
- systematized delusions
- hallucinations in other modalities

4) *Diagnosis of DLB unlikely in the presence of:*

- stroke, as per focal neurologic signs or appropriate imaging
- evidence on physical examination and investigation of any physical illness or other brain disorder sufficient to account for the clinical picture.

Adapted from McKeith IJ, Galasko D, Kosaka, et al. Consensus guidelines for the clinical and pathological diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop. *Neurology* 1996; 47: 1113-24.

cortex, due to the degeneration of neurons in the nucleus basalis of Meynert. The neurochemical abnormality leading to the parkinsonism seen is felt to be either due to disruption of the dopaminergic nigrostriatal paths, mesocortical paths, or more “downstream” pathology leading to dopaminergic disruption in the striatum itself.¹⁰

Clinical Features

Dementia with Lewy bodies. The core features of DLB form a triad of cognitive impairment, neuropsychiatric symptoms (especially visu-

al hallucinations), and parkinsonism. The current diagnostic criteria are listed in Table 2.¹³

Cognitive impairment is often the presenting feature of DLB.⁴ On testing, the pattern of dementia is a mixed cortical-subcortical dementia. Patients have prominent frontal-subcortical dysfunction with difficulty in attention, as well as executive function such as planning, sequencing and organization. A slowness of thought (bradyphrenia) is not uncommon.

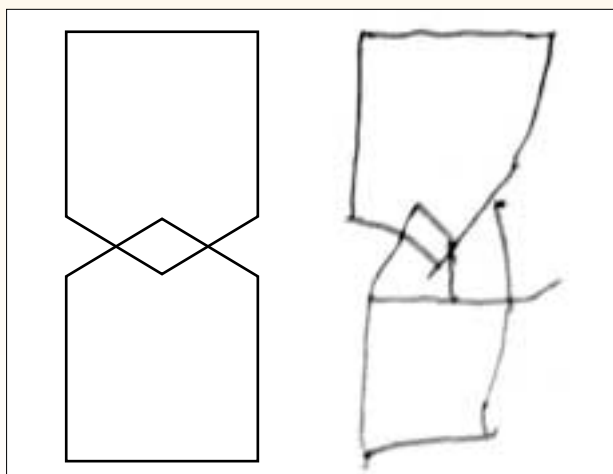
In addition to the frontal-subcortical dysfunction, patients also exhibit marked visuospatial

difficulties (Figure 2). A recent study compared AD patients to DLB patients on tests of visuospatial impairment.¹⁸ Patients were matched for age, sex and severity of cognitive decline. This study showed that the DLB patients had more difficulty not only with complex visual tasks, but also with tasks designed to look at elementary visual perception.

Ballard et al investigated distinguishing DLB from AD and vascular dementia (VaD) with the use of simple bedside tests.¹⁹ Using this battery of tests, DLB patients were significantly more

Figure 2

Visuospatial Dysfunction in DLB



Visuospatial dysfunction can be exemplified when a patient is asked to recreate a shape such as the one shown on the left above (resulting in a skewed version such as the one shown on the right).

impaired than AD and VaD patients on tests of visuospatial praxis. On tests of recent memory, DLB patients were less impaired than their AD and VaD counterparts.

Decreased tracer uptake in the occipital lobe on single photon emission-computed tomography (SPECT) and positron emission tomography (PET) scanning is associated with DLB, though the pathological correlate of this has yet to be elucidated.^{18,20} It is felt that this functional occipital lobe impairment is related to the visuo-perceptual difficulties seen in DLB.¹⁸

Attention in DLB is frequently impaired, and is often a component of the fluctuations in cognition that is one of the hallmarks of this disease. Fluctuations can be over minutes, days or even weeks

to months, and can include variation in attention and alertness, as well as variation in performance on cognitive testing.¹³ Fluctuations occur in 58% of patients at disease onset, and in 75% at some point during the course of the disease.²¹ The fluctuations usually do not follow a clear diurnal pattern.¹³ In a recent study evaluating tests of attention and reaction time, patients with DLB not only did worse than AD patients, they also exhibited a considerable variability in their reaction time consistent with second-to-second and minute-to-minute fluctuation.²²

Neuropsychiatric symptoms are also very common, with visual hallucinations being the most frequent manifestation. These hal-

lucinations are characteristically well formed, detailed and recurrent, often taking the form of small animals or people intruding in the person's home.¹³ One study found that hallucinations are present in 33% of patients at onset, and in 46% of patients at some time over the course of their disease,²¹ though rates as high as 80% have been reported.⁴ Frank hallucinations often co-exist with perceptual difficulties such as misidentifications and visual agnosias. The degree of insight retained into the hallucinations is variable. Patients may have hallucinations in other modalities, most commonly auditory (19% of patients at presentation).²¹ These tend to be well formed as well; for example, hearing the doorbell ring. Delusions can also happen, though they are less common. They tend to be bizarre and relate to recall of previous hallucinations and other perceptual disturbances.¹³

Parkinsonian symptoms. Parkinsonism (rest tremor, bradykinesia, rigidity, postural instability) is a core clinical feature of DLB. Approximately 26% of patients present with parkinsonism alone and a further 19% present with parkinsonian features in combination with other symptoms, such as dementia.³ By the end stages of the disease, only 4% to 25% of patients are free from parkinsonian motor symptoms.^{4,3}

Dementia of Parkinson's Disease

Cognitive impairment. The pattern of cognitive impairment seen in PDD is similar to that seen in DLB. Patients have difficulties with attention, as evidenced by poor performance on tests of vigilance and cognitive reaction time.²³ There is also some clinical evidence for fluctuations of attention.²³

Memory dysfunction is also similar to that found in DLB and different from that found in AD. It is generally less severe than in AD and, while patients may perform poorly on tests of free recall, they respond well to cues. Dysexecutive features are also prominent, with patients showing difficulties with problem-solving, set—shifting and maintenance. Patients also have difficulties with visuospatial tasks, especially “higher level” tasks such as visuospatial analysis and orientation judgement.²³ Language and praxis are relatively spared.

Neuropsychiatric symptoms are relatively common in PDD. Psychosis, including hallucinations and illusions, is found in 40% to 70% of patients with PDD.^{23,24} These symptoms can be difficult to differentiate from drug-induced psychosis, as the majority of these patients are taking at least one dopaminergic agent. Depression is also common. While neuropsychiatric features of hallucinations, delusions and depression can be present in patients with PD both

with and without dementia, they are more common in patients who have dementia.^{25,26}

Alzheimer's Disease with Parkinsonism

Characteristics of the extrapyramidal disorder. The most common extrapyramidal features found in AD are bradykinesia and rigidity.¹⁰ These features are usually bilateral in contrast to idiopathic PD, where an asymmetric and unilateral onset is most typical.

Approximately 26% of DLB patients present with parkinsonism alone and a further 19% present with parkinsonian features in combination with other symptoms, such as dementia. By the end stages of the disease, only 4% to 25% of patients are free from parkinsonian motor symptoms.

It is important to differentiate this rigidity from paratonia, which is extremely common in any type of dementia. Gait disturbance is the next most common extrapyramidal feature, including shuffling gait and impaired turning. Resting tremor in AD is rare.¹⁰ While extrapyramidal features can be found subtly in some patients in early AD, they are much more common as the disease progresses.¹¹

Differentiation Between DLB, PDD and AD with Parkinsonism

The clinical differentiation between PDD, DLB and AD can be

difficult, especially if a patient is presenting for the first time with a combination of dementia and parkinsonism. On a quite arbitrary basis, DLB is diagnosed if the dementia precedes the parkinsonian symptoms, or in the parkinsonism develops no more than one year prior to the cognitive impairment. If the parkinsonian symptoms have been present for more than 12 months prior to the onset of dementia, PDD is the preferred diagnosis. However, in most cases

of PD with dementia, the motoric parkinsonian symptoms are typically present for many years prior to the onset of noticeable cognitive decline.²⁷ Other differences that would make one favor a diagnosis of DLB over PD include the decreased prevalence of resting tremor (55% vs. 85%),³ the decreased responsiveness of motor symptoms to L-dopa, the decreased tolerability of L-dopa secondary to psychiatric side effects, and the occurrence of spontaneous (as opposed to drug-induced) visual hallucinations. It is felt that, given the similarity of pathology and clinical symp-

toms, PD and DLB likely lie upon a continuum, with clinical manifestations dependent on the extent and location of LB disease.¹²

The differentiation of DLB and

PDD from AD is easier. Parkinsonism is usually a late feature in AD, preceded by cognitive decline for many years. The pattern of dementia is different, with prominent episodic memory loss

early in the course of the disease. Visual hallucinations are relatively rare, and when they occur, they tend to be later in the course of the disease.

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