Are Parkinson’s Disease With Dementia and Dementia With Lewy Bodies the Same Entity?

Dag Aarsland, MD, PhD, C. G. Ballard, MD, MRCpsych, and Glenda Halliday, PhD

ABSTRACT

The diagnosis of Parkinson’s disease with dementia (PDD) or dementia with Lewy bodies (DLB) is based on an arbitrary distinction between the time of onset of motor and cognitive symptoms. These syndromes share many neurobiological similarities, but there are also differences. Deposition of beta-amyloid protein is more marked and more closely related to cognitive impairment in DLB than PDD, possibly contributing to dementia at onset. The relatively more severe executive impairment in DLB than PDD may relate to the loss of frontohippocampal projections in DLB. Visual hallucinations and delusions associate with more abundant Lewy body pathology in temporal cortex in DLB. The differential involvement of pathology in the striatum may account for the differences in parkinsonism. Longitudinal studies with neuropathological and neurochemical evaluations will be essential to enable more robust comparisons and determine pathological substrates contributing to the differences in cognitive, motor, and psychiatric symptoms. (J Geriatr Psychiatry Neurol 2004; 17:137-145)

Keywords: cognition; dementia; Lewy bodies; neurochemistry; neuropathology; parkinsonism

Dementias associated with cortical Lewy bodies are traditionally classified as dementia with Lewy bodies (DLB), characterized by parkinsonism, visual hallucinations and cognitive fluctuations, or Parkinson’s disease with dementia (PDD). Overall, DLB accounts for about 20% of late-onset dementia cases, and dementia develops in the majority of cases with a diagnosis of PD. As outlined below, there are clinical and neurobiological similarities between DLB and PDD patients. The distinction between the conditions as operationally defined within the standardized clinical criteria depends entirely on the duration of parkinsonism prior to dementia. The consensus criteria for a clinical diagnosis of DLB state that a diagnosis cannot be made if parkinsonian symptoms developed more than 1 year before the onset of dementia (although proposed recent changes to the criteria may alter this to making the diagnosis according to whether parkinsonism or cognitive impairment arises first). This raises several key conceptual questions; for example, are these conditions distinct or part of the same spectrum? If they are distinct conditions, is an arbitrary cutoff (either 1 year or which symptom presents first) a meaningful distinction between clinical entities with different clinical presentations? Addressing these issues is critical to taking forward our understanding of this spectrum of conditions, establishing biological markers, determining prognostic indicators, and, most important, designing appropriate intervention studies and developing treatment paradigms across the dementias associated with cortical Lewy bodies.

In the current article, key issues pertaining to DLB and PDD are reviewed, and the similarities and differences in the clinical profile (cognitive deficits, neuropsychiatric symptoms, and parkinsonism), imaging, genetic predisposition, neurochemistry, and neuropathology are discussed to enable some conclusions about the relationship of the 2 conditions and to offer some suggestions for critical future research. Direct comparative studies of patients with PDD and DLB are necessary to explore the relationship between these 2 syndromes. We searched the MEDLINE using Parkinson disease and dementia
with Lewy bodies as search (title) words, as well as searching book chapters and abstracts that were available to us.

Methodological Issues
Direct comparative studies are the preferred choice to explore the relationship between DLB and PDD, but several methodological issues need to be borne in mind when considering such studies. Critical issues include the selection of subjects (ie, whether community based or hospital based); the severity of dementia; whether subjects were matched for severity of dementia, sample size, sensitivity, and other psychometric properties of the tests used to characterize the patients; and diagnostic criteria and methods of diagnosis (eg, diagnosis based on autopsy, prospective clinical assessment, or retrospective chart review). Many studies comparing neuropathology or chemistry in PD and DLB did not specify whether PD patients had dementia. Because these 2 groups differ markedly in this regard, the interpretation of results from most of these studies is difficult.

COMPARATIVE STUDIES OF STRUCTURAL NEUROPATHOLOGY IN PDD AND DLB

Atrophy and Cortical Cell Loss
Although DLB and PDD cannot be differentiated based on the pattern of brain atrophy, they both have limited atrophy compared with other dementia syndromes. There is no substantial subcortical atrophy in pathologically confirmed cases, although a small reduction in the volume of the putamen has been documented in vivo. Mild frontal lobe atrophy and medial temporal lobe atrophy are consistent features. Temporal lobe and occipital atrophy has been documented in some clinical cohorts, but these regions are spared in pathologically confirmed cases, unless they also have Alzheimer's disease.

In both DLB and PDD, there is limited cortical cell loss, even in frontal regions. Medial temporal lobe structures are abnormal in both DLB and PDD, although hippocampal cell loss may differentiate DLB from PDD. In both conditions, however, the severity of hippocampal atrophy is less marked than that seen in Alzheimer's disease. Both Lewy body disorders have significant but similar atrophy and pathology in the amygdala. In contrast, hippocampal pyramidal neurons innervating the frontal cortex selectively degenerate in DLB.

Amount of Lewy Body Pathology
In many cortical regions, the amount of Lewy body pathology does not differentiate DLB from PDD or PD, although more temporal lobe Lewy bodies occur in DLB. The lack of an association between the amount of cortical Lewy body pathology and the timing of dementia in Lewy body diseases is disconcerting but well documented and suggests that Lewy bodies are not the only pathology contributing to these dementia syndromes. However, subtle differences in the type and severity of pathology between DLB and PDD influence clinical phenotype. The increase in temporal lobe Lewy bodies in DLB correlates with the early occurrence of the characteristic well-formed visual hallucinations rather than dementia duration or severity. In contrast, increasing Lewy body densities in limbic and frontal cortices in PDD correlate with the severity of dementia. This dichotomy of regional Lewy body pathology suggests that the disease processes driving DLB and PDD differ.

Other Contributing Pathologies
Most cases of DLB can be differentiated from those with PDD by their substantial deposition of cortical amyloid-beta (Aβ), even in the absence of significant neurofibrillary tangle formation. This further substantiates different disease processes between DLB and PDD, with the density of Aβ-positive plaques in DLB equivalent to that found in Alzheimer's disease. Although the amount of Aβ deposition and cortical Lewy bodies correlates with dementia severity in DLB, this does not seem to be the case in PDD. In a prospective clinicopathologic study of population-based samples of patients with dementia and with PD, Lewy body formation but not neuritic plaque pathology contributed to dementia severity in PD, whereas both pathologies contributed to dementia severity in DLB cases. Thus, the amount of Lewy body formation does not relate to whether dementia occurs early (ie, DLB) or late (ie, PDD) in the disease course but correlates with the severity of dementia in PDD. Similar findings have been reported in other studies, although in some studies, Alzheimer-type pathology was reported to be significantly associated with dementia in PD.

COMPARATIVE STUDIES OF NEUROCHEMICAL CHANGES IN PDD AND DLB

Most neurochemical studies of DLB and PD have focused on the cholinergic and dopaminergic neurotransmitter systems, which may influence a range of key clinical symptoms such as cognition, attentional fluctuations, hallucinations, delusions, and parkinsonism.

Dopaminergic Deficits
Caudate nucleus dopamine loss is pronounced in both DLB and PD, with subtle differences in the symmetry and rostrocaudal gradient in DLB and PDD consistent with the subtle differences in the presentation of parkinsonian symptoms (see below). However, direct comparison of the degree of cell loss in the dopaminergic substantia nigra in PD, PDD, and DLB suggests a similar pattern of cell loss in the dopaminergic substantia nigra. The degree of nigral loss is >60% in all subjects and correlates with disease duration, which is longer in
PD and PDD than in DLB. Greater loss of striatal dopamine is therefore observed in PD compared with DLB, with more abundant residual neuritic pathology observed in DLB than in PD. In PD but not in DLB, there is a compensatory increase in striatal D2 receptors and dopamine turnover, with PDD patients having intermediate D2 binding between DLB and PD. The consistent dopaminergic deficit is being translated into a useful clinical imaging tool for differentiating DLB from Alzheimer’s disease and other dementia syndromes.

**Cholinergic Deficits**

Neurochemical studies consistently find marked cortical cholinergic deficits in both PDD and DLB, more marked than in PD cases without dementia, suggesting that the amount of cholinergic cell loss in the basal forebrain cholinergic neurons supplying the majority of cortical acetylcholine is similar in DLB and PDD. However, differential involvement of the cholinergic system in DLB and PD has also been reported. Cholinergic markers are reduced in the striatum in patients with DLB but not in those with PD. Furthermore, in selected thalamic nuclei, marked reductions were found in PDD and in DLB patients with but not without parkinsonism. In DLB but not in PDD, there is a correlation between visual hallucinations and cholinergic deficits in the temporal cortex.

The impact on cortical cholinergic receptors is similar in PDD and DLB, with increased muscarinic binding and a considerable reduction in nicotinic binding, although in the insular cortex the reductions were more marked in PDD than in DLB. Further studies indicate a possible association between impaired consciousness and upregulation of nicotinic α4β2 nicotinic receptors in the temporal cortex.

In a study comparing muscarinic receptor binding within the striatum in DLB and PD patients, M1 receptors were significantly reduced in DLB but not in PD patients. However, the 3 PD patients with dementia had binding levels intermediate between PD and DLB. In both DLB and PD, there is a similar reduction in striatal nicotinic binding consistent with these receptors being located on dopaminergic terminals. For a more comprehensive review of cholinergic changes in DLB and PDD, see references in this issue.

**GENETICS IN PDD AND DLB**

So far, there are insufficient data to make meaningful conclusions regarding the similarities and differences in the genetic factors predisposing to PDD and DLB.

**Causal Genes**

Recent studies have identified several loci involved in the development of PD. In rare families, point mutations in the alpha-synuclein gene (SNCA) give rise to autosomal dominant PD. Although parkinsonism is usually the presenting feature in familial PD, in some individuals dementia is the presenting feature, and these cases show extensive cortical Lewy body pathology. Thus, at least in some cases, PD and DLB are genetically closely related. In addition, as many as 5% of cases of early-onset (<60 years) PD and PDD appear to be due to triplication or duplication of SNCA. Although there is some evidence indicating that genetic factors contribute to DLB, the genes predisposing to PD have not yet been systematically investigated in DLB.

**Modifying Genes**

The apolipoprotein ε4 allele has a higher frequency in DLB than in age-matched controls and is associated with a more rapid progression of cognitive impairment in affected individuals. Similarly, a possible association between the apolipoprotein ε4 allele and dementia in PD has been reported although other studies did not find such an association.

**COMPARATIVE STUDIES OF CLINICAL FEATURES IN PDD AND DLB**

**Cognitive Deficits**

The cognitive profile of both PDD and DLB has been characterized as featuring visuospatial, attentional, and executive impairment with relatively less memory impairment. This is based on studies comparing DLB and PDD patients with patients with Alzheimer’s disease. The overall profile of cognitive deficits is quite similar in the 2 syndromes (details of studies in Table 1), with both PDD and DLB patients exhibiting significantly more marked executive and less severe memory deficits than did those with Alzheimer’s disease. Interestingly, fluctuating attention, a key feature of DLB, was found in both DLB and PDD patients but not in patients with Alzheimer’s disease or PD without dementia, and less marked fluctuation of attention was also found in DLB patients without parkinsonism. An additional study comparing pentagon copying in patients with DLB and PDD suggested a similar severity of impairment in the 2 conditions and a pattern of errors indicating executive dysfunction. A further study, although suggesting marked executive dysfunction in both PDD and DLB, showed that in the context of mild dementia, patients with DLB had a significantly lower score on the Dementia Rating Scale Conceptualization subscale than did PD patients, suggesting that executive impairment is more pronounced in DLB than in PD patients with mild dementia. Overall, however, the profile of cognitive impairments in DLB and PDD appears to be similar and distinct from Alzheimer’s disease but with some subtle differences, including more marked executive dysfunction in DLB.
Psychiatric Symptoms
Psychiatric symptoms are common in all dementia syndromes, but a characteristic psychiatric profile has been reported in patients with DLB and PDD (Table 2). Visual hallucinations and delusions are much more common in DLB than in Alzheimer’s disease, occurring in 60% to 70% of patients with DLB,50,51 whereas in PDD, hallucinations (45%-50%) but not delusions (15%-24%) were more common than in Alzheimer’s disease.51,52 Another distinguishing feature of these syndromes is the high frequency of REM sleep disorders, which are also much more common in DLB and PDD than in other dementias (see Boeve, this issue).53 Other symptoms commonly reported, such as depression, apathy, and anxiety, are common in other dementias, although several studies suggest a higher frequency of depression in DLB,50,51 consistent with the high frequency of depression in PD.54 Comparisons of the phenomenology of psychotic symptoms in DLB and PDD show that the content of the hallucinations and delusions was indistinguishable.51,52 However, the frequency of hallucinations51,52 and delusions52 was significantly higher in DLB patients than in PDD patients.

Parkinsonism
It has frequently been suggested, based largely on anecdote, that parkinsonism is less severe in DLB than in PD. However, comparative studies have usually not supported this view, finding similar or even more severe symptoms in DLB than in PD (Table 3). A similar profile of parkinsonism has also been reported,55 although in one study DLB patients had more symmetrical parkinsonism and relatively higher rigidity and lower resting tremor scores than did PD patients.56 Importantly, these studies usually included subjects with and without dementia. In the most detailed comparative study of parkinsonism to date, Burn et al found that DLB patients had less severe parkinsonism than did PDD patients but a similar severity of motor deficits to PD patients without dementia.57 Postural instability and gait difficulties, predominantly mediated by non-dopaminergic deficits, were more pronounced in DLB and PDD patients than in PD patients without dementia, whereas the opposite was found for tremor. Although there are no direct comparative studies, the rate of progression of rating scales of parkinsonism appears to be about 9% per annum in DLB and PD.58,59 Overall, therefore, severity of parkinsonism is similar in DLB and PD and progresses at the same rate, although there appears to be relatively more nondopaminergic symptoms and less asymmetry in DLB, consistent with neurochemical findings.

Treatment Studies
Frequently, DLB patients experience severe sensitivity reactions in response to neuroleptic drugs (NSR),60 and preliminary evidence suggests similar reactions in a considerable proportion of PDD patients, although occurring less commonly than in DLB patients.61 The symptoms of severe NSR experienced by the respective groups of patients are very similar, although it appears that PDD patients are less likely to die within a few months of neuroleptic exposure. Two randomized placebo-controlled studies support the use of clozapine for PD patients with psychosis (with no or mild dementia), but undertaking such trials in DLB is problematic because of the high frequency of severe NSR and the high related mortality rates. Recent reports of higher mortality rates and risk of cerebrovascular incidents in elderly patients with dementia associated with risperidone and olanzapine underline the potential high risk of these agents.

Favorable symptomatic improvement is seen in both DLB and PDD following cholinesterase inhibitor therapy (see articles in this issue). We are aware of only one open-label study comparing the treatment effects in PDD and DLB. Minett et al62 showed a similar improvement on cognition and psychiatric symptoms on donepezil in DLB and PDD patients and no change in parkinsonism in both groups, although PDD patients showed a greater worsening of psychiatric symptoms after withdrawal of the drug.

Unfortunately, there are no systematic reports of the response to levodopa treatment in DLB patients, and no published comparisons exist. Theoretically, the high proportion of DLB patients with predominantly non-dopaminergic motor deficits suggests that such therapy would be less effective in DLB patients than in PD patients. Preliminary evidence from ongoing studies supports this hypothesis.63

DISCUSSION

Summary of Major Findings
Although methodological shortcomings of comparative studies of DLB and PDD make interpretation difficult, there is evidence of considerable overlap in the clinical, neurochemical, and pathological features of DLB and PDD. Both have parkinsonism, similar cognitive deficits, similar patterns of atrophy, similar amounts of Lewy body pathology, and similar substantial cholinergic and dopaminergic deficits that appear amenable to similar treatments. However, although there are many similarities in the type and frequency of clinical features diagnostic for DLB and PDD, the severity of executive dysfunction, frequency of visual hallucinations and delusions, and relative predominance of postural instability/gait disorders are significantly greater in DLB than in PDD. Subtle neurochemical and pathological differences are likely to subserve these differences. Executive dysfunction may relate to the loss of the hippocampal projection to the frontal lobe in DLB but not in PD, and more severe Lewy body pathology may relate to the high-
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<td>Aarsland et al66</td>
<td>35</td>
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<td>74</td>
<td>23.9b and 17.7</td>
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<tr>
<td>Noe et al67</td>
<td>15</td>
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<td>21.8b</td>
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<td>Cahn-Weiner et al70</td>
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<td>112*</td>
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<td>Ballard et al78</td>
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Note: DRS, Dementia Rating Scale; BSRT, Buschke Selective Reminding Test; BVRT, Benton Visual Retention Test; VF, Verbal Fluency Test; BNT, Boston Naming Test; WAIS-R, Wechsler Adult Intelligence Scale-Revised; BDAE, Boston Diagnostic Aphasia Examination; RDT, Rosen Drawing Test; MMSE, Mini Mental State Examination; WMS-R, Wechsler Memory Scale-Revised; WRMT, Warrington Recognition Memory Test; CDR, Cognitive Drug Research computerized battery (tests of simple, choice, and cognitive reaction times).

*a. Not demented.
b. The measure of the severity of cognitive impairment was the MMSE.
c. For this study, the age is the age at onset of dementia and the severity of cognitive impairment is the final MMSE score.
d. The measure of the severity of cognitive impairment was the IQ test.
e. The measure of the severity of cognitive impairment was the DRS.
f. The scoring system of the clock drawing was from Rouleau.
g. The scoring system of the clock drawing was from Bourke.
*h. Modified Stern et al.  Modified Stern et al.
er frequency of psychiatric features in DLB. The differential pattern of parkinsonian features in PD and DLB is in accordance with the differential striatal changes, with changes in PDD patients being intermediate between those found in DLB and PD patients.

Of course, the most obvious difference is the early onset of dementia in DLB compared to that of PDD. The explanation for this relationship may be the pathological feature that occurs in DLB and not in PDD, the presence of substantial cortical Aβ protein deposition. Thus, DLB is similar to Alzheimer’s disease in that it has 2 major pathologies, cortical Aβ and Lewy bodies in DLB versus cortical Aβ and neurofibrillary tangles in Alzheimer’s disease, whereas PDD has mainly Lewy body pathology and a late onset of dementia.

**Nosological Aspects**

A classical nosological definition of a disease includes common etiology, pathophysiology, clinical presentation, and course. Although the current evidence demonstrates remarkable similarities between DLB and PDD, there are also both subtle and marked differences. The available evidence suggests that the heterogeneity within the 2 syndromes may be greater than the differences between them. For example, some patients who develop parkinsonism will develop dementia within a year and be classified as DLB, others will develop a dementia syndrome within a 5- to 10-year period and thus be classified as PDD patients, whereas some patients with PD will remain cognitively intact for decades. Current diagnostic classification of patients with parkinsonian dementias is based only on the timing of motor and cognitive symptoms with some data supporting this distinction (see above). We recommend further research to provide more empirical evidence for the classification.

There is significant biological overlap between DLB and PDD, and it will be important to determine the reasons for such overlap, as well as the neurobiological dif-
ferences. The occurrence of cortical Aβ plaque pathology adds further complexity to the interpretation. Two recent studies indicate that DLB patients with marked neurofibrillary tangle pathology (ie, coexisting Alzheimer’s disease) are less likely to present with the typical features of DLB (including impaired consciousness and parkinsonism). There is considerable debate as to the classification of patients with coexisting Alzheimer’s disease and DLB (3 substantive pathologies), as the DLB syndrome appears to be less distinct in these cases.

There are 4 possible models that could be used to classify DLB and PDD. (1) They could be considered as distinct conditions. (2) They could be considered as part of a spectrum of dementia related to cortical Lewy body disease. (3) Both DLB with parkinsonism and PDD could be considered as a distinct condition but separate from DLB without parkinsonism and PD without dementia. (4) They could be considered as part of a spectrum of Lewy body– and Alzheimer-type pathology. The commonality of the presenting symptoms, treatment response, and many neuropathological/neurochemical substrates would seem to best support a spectrum model, although the additional cortical Aβ deposition in DLB suggests important differences subserving dementia at onset. The paucity of direct comparisons, however, makes conclusions speculative, and further comparative studies are a high priority. Longitudinal studies with neuropathological and neurochemical evaluations are essential to enable more robust comparisons and to determine the impact on presentation of the individual pathological substrates that may contribute to cognitive, motor, and psychiatric symptoms.

References
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