tauopathy or other CNS degeneration. A movement disorders specialist would be better able to rule out progressive supranuclear palsy or other Parkinson's plus syndromes.

Gonzalo J. Revuelta and Carol F. Lippa
Drexel University College of Medicine
Department of Neurology, Philadelphia, U.S.A.
Email: Carol.Lippa@DrexelMed.edu

Parkinson's disease dementia and dementia with Lewy bodies: different aspects of one entity

Introduction

The combination of dementia and parkinsonism is common and distressing, and dementia associated with Parkinson's disease (PDD) and dementia with Lewy bodies (DLB) are the most common causes. By definition, in PDD, dementia develops after more than one year with parkinsonism, whereas in DLB, dementia occurs before, simultaneously with, or within one year of the onset of parkinsonism. Whereas there are obvious clinical challenges in defining the exact timing of onset of two insidiously developing syndromes, most patients can easily be clinically allocated to either the PDD or DLB group. However, the third report of the DLB Consortium demonstrated the unresolved issues in the relationship between these two disorders, since on the one hand the overall clinical and pathological similarities were underlined, both being Lewy body diseases (LBD), but at the same time it was proposed that the two syndromes should be distinguished in research settings, and further studies exploring these boundary issues were recommended.

In this debate, we will review recent studies comparing clinical and neurobiological features in PDD and DLB, and argue how they support the hypothesis that these syndromes can best be considered as different aspects of one entity. However, we will also argue that the situation is more complex, and that there is considerable variation between, as well as within, the two syndromes, and that much work needs to be done to clarify the relationship between brain changes, genetics and the clinical course of these syndromes. Such understanding is crucial to improving the management of these frail and vulnerable patients.

Preclinical

Genetics

One key factor for considering whether two syn dromes should be lumped together or not is whether they have a common etiology. In Parkinson's disease (PD), both environmental and genetic factors likely contribute, whereas the etiology of DLB is not known. Whereas little is yet known regarding the genetics of DLB, exciting recent studies have identified several genes involved in the development of PD, including the alpha-synuclein (SNCA), parkin, DJ-1, LRRK2, PINK1 and other genes. There are several reports of familial PDD, and also some reporting familial DLB (Kurz *et al.*, 2006). The level of clinical detail varies among the reports, and the underlying genetic contribution has not always been reported. Finally, families with both DLB and PDD phenotypes have been reported. Recently, a three-generational Belgian family with different phenotypes involving dementia and/or parkinsonism (Bogaerts *et al.*, 2007) was described, with significant linkage to 2q35-q36. Together, these reports support the hypothesis of a common genetic underpinning of DLB and PDD.

Genes leading to amyloid deposition, such as APOE ∈4 and BuChE k-variant may also influence the phenotype of LBD. Whereas APOE ∈4 has emerged as a risk factor for Alzheimer's disease (AD), inconsistent findings regarding the effect of APOE genotype on cognitive decline in PD have been reported (Kurz *et al.*, 2006), whereas in DLB, the presence of an APOE ∈4 allele alone appears to accelerate the progression of cognitive decline (Ballard *et al.*, 2001). BuChE genotype is associated with subcortical pathology and executive dysfunction, with an altered rate of cognitive decline (Perry *et al.*, 2003) and treatment response to cholinesterase inhibitors associated with both DLB and PDD (O'Brien *et al.*, 2003). Interestingly, in mild cognitive impairment, the combination of one APOE ∈4 allele and the k-variant of BuChE was associated with a more rapid cognitive decline and progression to Alzheimer's disease (AD), but the impact on the course of disease in PD and DLB is not known.

Cerebrospinal fluid

Whereas pathology is considered to be the gold standard for establishing the etiology of dementia,

analyzing cerebrospinal fluid (CSF) provides clues as to brain changes associated with the dementia syndrome during the course of disease. Several studies of CSF have consistently shown characteristic changes of amyloid-beta and tau peptides in AD, but the few studies involving DLB and PDD have shown conflicting results. The iIncrease of an oxidated variant of amyloid-beta-peptide 1–40 relative to the sum of amyloid-beta-peptides was found to be higher in DLB than PD, whereas other species did not differ (Bibl *et al.*, 2006). In a recent study, significantly reduced amyloid-beta-peptide 1–42 was reported in DLB compared to PDD, whereas total and phosporylated tau did not differ significantly (Parnetti *et al.*, 2008), supporting the hypothesis that the amyloid deposition contributes more to dementia in DLB than in PDD, although this may be a quantitative rather than a qualitative difference.

α-synculein is the pathological hallmark of DLB and PDD, and appears to be the pathological substrate most closely related to progressive cognitive decline in these individuals. α-synculein is therefore a potentially attractive biomarker, and although there are some methodological difficulties, it has been successfully measured in the CSF. Interesting preliminary work has reported a significant decrease of α-synuclein in the CSF of PD patients compared to controls (Tokuda *et al.*, 2006), and ongoing work in our laboratory based on semi-quantification using Western blotting has also demonstrated significant reductions of α-synuclein in the CSF of DLB patients (DLB: 1792.6 ± 3318.8, controls: 7981.3 ± 6564.7, $z = 3.2$, $p = 0.001$). It would hence appear that there are reductions of CSF α-synuclein in both PD and DLB, but as there are no studies specifically focusing on PDD patients and no direct comparisons between DLB and PDD it is as yet unknown whether the magnitude of the change differs between the two conditions.

Electrophysiology

Characteristic electroencephalogram (EEG) changes have been reported in patients with DLB, such as more slowing and frequency variability. Two recent studies included both PDD and DLB. In one study of patients with early and mild dementia (Bonanni *et al.*, 2008), patients with DLB and PDD had more posterior slowing and frequency variation than AD and healthy control subjects. At baseline, the changes were more common and severe in DLB than in PDD, although at the two-year follow-up, the changes in PDD had become more pronounced. Interestingly, two subgroups of PDD with and without cognitive fluctuations were identified, with EEG changes similar to the DLB group in PDD with fluctuations, but not in those without. In contrast, in a study assessing mismatch negativity (MMN), a component of the auditory event-related potential (ERP) considered to represent a basic automatic change detection system, pronounced changes with reduced MMN latency and areas were found in PDD, but not in DLB or AD (Brønnick *et al.*, 2008).

Imaging

Structural

Using structural magnetic resonance imaging (MRI), the typical finding in DLB is relative preservation of hippocampus and medial temporal lobe volumes in DLB in comparison with AD. Other cortical and subcortical changes have also been reported in DLB, including the substantia innominata, hypothalamus and dorsal midbrain (Whitwell *et al.*, 2007). Similar changes have been reported in PDD. However, the two studies comparing MRI in PDD and DLB have reported conflicting findings, with one reporting no differences (Burton *et al.*, 2004), while the other found more pronounced cortical atrophy in DLB than in PDD (Beyer *et al.*, 2007).

Functional

A characteristic pattern of occipital and parietal hypoperfusion – the so-called horse-shoe sign – has been demonstrated in DLB, and similar findings have been reported in PDD (Colloby and O'Brien, 2004). Scintigraphy with ^{123}I-metaiodobenzylguanidine (MIBG) enables the quantification of post-ganglionic cardiac sympathetic innervation, and several studies have demonstrated reduced cardiac compared to mediastinal uptake in DLB and PD, as opposed to AD (Taki *et al.*, 2004).

Reduced dopamine transporter in the caudatum and putamen is a marker of loss of dopaminergic neurons in the substantia nigra, and can be detected by dopaminergic PET or SPECT, using ligands specific for the dopamine transporter, such as ^{123}I-ß CIT and ^{123}I-FP-CIT. Such studies have shown reduced striatal dopamine transporter uptake in PD and DLB, but not AD. However, differences in the regional distribution in DLB and PDD have been demonstrated (O'Brien *et al.*, 2004).

Neurochemistry

The majority of neurochemical studies of PDD and DLB have explored the dopamine and acetylcholine systems, and overall, the findings are similar. Marked cholinergic deficits have been reported in both PDD and DLB, but with the greatest cholinergic deficits evident in patients with longstanding PD prior to the onset of dementia

(Ballard *et al.*, 2006). Similar receptor changes have also been reported in DLB and PDD, with increased muscarinic (Colloby *et al.*, 2006) and reduced nicotinergic binding.

Although nigro-striatal dopamine changes occur in both syndromes, the severity and distribution of changes differ, with more marked nigral cell loss in PDD than DLB, although this may be related to differences in disease duration. Importantly, there is a post-synaptic dopaminergic up-regulation in PD, but not in DLB, which may translate to the increased risk for neuroleptic sensitivity reactions in this group (Piggott *et al.*, 1998). However, the interpretation of this literature is difficult since the patient groups are usually not matched for demographic or key clinical features such as duration and disease severity, and it is not always clear whether the PD patients have dementia or not. In addition, comparisons of key neurochemical systems such as serotonin, noradrenalin and glutamate have not yet been performed, and the association between neurochemical changes with clinical symptoms has rarely been explored. Preliminary data from our group show significantly higher frontal 5-HT_{1A} receptor binding density in DLB compared with PDD, suggesting a distinct neurochemical feature of the two dementias (Francis and Perry, 2007). Finally, one major animal model for PD, suggesting that dysfunction of the ubiquitine-proteasome system is a key element in the pathophysiology of PD, was recently found to be a relevant model also for DLB (Macinnes *et al.*, 2008).

Neuropathology

Overall, the pathological characteristics of PDD and DLB are similar, with less neuronal and synaptic loss than in AD, high density of cortical Lewy bodies, and presence of senile plaques and neurofibrillary changes. Most studies have reported more pronounced cortical changes in DLB compared to PDD, including Lewy bodies, senile plaques and neurofibrillary tangles (Ballard *et al.*, 2006). An interesting recent study found differential expression of α-synuclein, parkin and synphilin isoforms in different Lewy body diseases, suggesting the possibility that different molecular mechanisms lead to similar neuropathological changes, and hence clinical phenotypes (Beyer *et al.*, 2008).

Clinical

Similar clinical characteristics have been reported in DLB and PDD, such as frequent visual hallucinations, REM-sleep behavior disturbance, fluctuating cognition, parkinsonism, and a cognitive profile characterized by relatively more pronounced attentional, executive and visuo-spatial abnormalities than in AD, and less severe memory abnormalities (Aarsland *et al.*, 2004). However, within this overall picture of similarities, there are subtle differences. In DLB patients, visual hallucinations and cognitive fluctuations are usually reported to be more common than in PDD. In mild dementia, relatively more severe executive impairment has been found in DLB. In contrast, more pronounced auditory attentional disturbances were found in PDD compared to DLB (Brønnick *et al.*, 2008). The finding of more pronounced differences between DLB and PDD in early rather than later disease is consistent with the findings on EEG reported recently (Bonanni *et al.*, 2008).

Of note, subgroups within the DLB and PDD syndromes have been reported. DLB patients with marked concurrent neurofibrillary tangle pathology (Braak stage 5 and 6) do have a different clinical profile with less parkinsonism, fewer cognitive fluctuations and fewer neuropsychiatric symptoms compared to those with no or mild tangle pathology (Ballard *et al.*, 2004). Similarly, PDD patients with and without cognitive fluctuations have markedly different EEG patterns (Bonanni *et al.*, 2008), those with fluctuations having a pattern similar to DLB whereas those without fluctuations have a pattern similar to AD and normal controls. Finally, PDD patients with hallucinations have a more rapid cognitive decline than those without (Burn *et al.*, 2006b).

Course and drug response

Few longitudinal studies of DLB and PDD exist, and none have directly compared the disease course. Less response to L-dopa has been found in DLB than in PD, although the response in PDD is rather similar to DLB (Molloy *et al.*, 2006). A key pharmacological feature of LBD is the very high risk of developing marked sensitivity reactions to neuroleptic drugs, which is more common in DLB than in PDD (Aarsland *et al.*, 2005a). The limited evidence does not indicate different response to cholinergic drugs in DLB and PDD.

Discussion

As outlined above, a large number of studies within a wide variety of clinical and pre-clinical areas have convincingly demonstrated the similarities of DLB and PDD, thus supporting the hypothesis that they represent one disease entity. However, there is also emerging evidence of subtle differences, particularly early in the course of the disease, both with regards to clinical symptoms and underlying brain changes, suggesting that PDD and DLB, and

PD, represent different aspects of a spectrum of LBD. Several arguments, such as the differences within the two syndromes, suggest that the question is not lumping or splitting, but rather that we need to move beyond this and consider the key factors influencing the development of brain changes and clinical symptoms in LBD, such as concurrent AD, cross-talk between proteins, genes, and the effect of age.

Information derived from genetics

Different mutations, or dupli- or triplication of the SCNA gene, have been shown to present a spectrum of phenotypes within the overall LBD type. There is emerging evidence that in LBD, the clinical phenotype, i.e. PD, PDD or DLB, is dependent on SNCA gene dosage and corresponding protein levels, with earlier disease onset and more widespread symptoms related to triplication compared to duplication of SNCA. In addition, different isoforms of SCNA and other PD genes may influence pathology and phenotype (Beyer *et al.*, 2008). These and other recent data re-emphasize the genetic heterogeneity, and also that one genotype can lead to a mixed phenotype.

The finding that people with PDD and DLB not only have similar clinical symptoms but also have similar underlying brain changes, and that both phenotypes can be found in the same families with similar genotype, strongly implies that the arbitrary distinction between PDD and DLB based upon presentation of parkinsonism one year prior to dementia does not reflect molecular biology of the disease process.

Interaction of age and disease mechanisms

There is evidence suggesting an interaction between age and disease progression in PD, with older patients with PD having a faster motor decline, poorer drug response, more severe gait and postural disturbances, and more cognitive decline compared to younger patients. According to one hypothesis, there is a biological interaction between PD and age on brain lesions leading to postural and gait disturbance and dementia, but not on tremor and rigidity (Levy, 2007). Thus, it is possible that in addition to the subtle genetic differences – such as the dosage level of SCNA change, different point mutations in specific genes, and different isoforms – an effect of age can be added. The interaction between age and disease factor may influence the phenotype of LBD, i.e. whether a pure motor syndrome (PD), a motor syndrome followed by cognitive decline and dementia (PDD), dementia and parkinsonism occurring simultaneously without significant AD pathology (pure DLB), or dementia followed by parkinsonism due to a combination of α-synuclein, tau and amyloid pathologies will develop.

The arbitrary distinction based on the relative timing of parkinsonism and dementia is highlighted by many studies demonstrating considerable variation *within* DLB and PDD. For example, differences have been reported based on PDD with and without cognitive fluctuations (Bonanni *et al.*, 2008) and according to the time from onset of PD to dementia (Ballard *et al.*, 2006). Similarly, based on the presence or absence of Alzheimer-type pathology, DLB patients have been classified pathologically into pure or common DLB (Ballard *et al.*, 2006). Furthermore, due to the marked genetic and pathological heterogeneity, the notion that PD is one disease has been challenged (Calne and Mizuno, 2004). Thus, although the current evidence favors the hypothesis that DLB and PDD are entities on a spectrum of Lewy body disease, the available data do not suggest that any specific cut-off threshold based upon the relationship between the onset of dementia and the onset of PD would help distinguish distinct and meaningful biologic entities. Thus, more research is needed. In particular, the clinically meaningful question of how the various brain changes relate to clinical course and treatment response needs to be explored.

Finally, in addition to discussing the relationship between PD, PDD and DLB, it is also important to discuss the overlap of LBD and AD. Genetic studies have shown the relevance of the combined APOE and BuChE genotypes for the clinical course and pathology of both LBD and AD (Lane *et al.*, 2008) In addition, important studies have revealed a major interaction of the key proteins involved in these diseases: amyloid aggregates may enhance the aggregation of α -synuclein (Lashley *et al.*, 2008), and there is a reciprocal interaction between tau and α -synuclein interaction (Giasson *et al.*, 2003). These unresolved issues have implications not only for diagnosis and classification, but also for the underlying neuropathology and, ultimately, for the development of novel, mechanism-based treatment targeted towards individual patients.

Dag Aarsland,[1] E. Londos[2] and Clive Ballard[3]

[1]The Norwegian Centre for Parkinson's Disease Stavanger University Hospital, Norway and Institute of Clinical Medicine, University of Bergen, Norway
Email: daarsland@gmail.com

[2]Clinical Memory Research Unit, Malmö University Hospital, Lund University, Malmö, Sweden

[3]Wolfson Centre for Age-Related Diseases, King's College London, U.K.