Chapter 2

Parkinson's disease and the spectrum of Lewy body disease

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History

Parkinson's disease (PD) and dementia with Lewy bodies (DLB) are two common presentations of a single, underlying disease process that is thought to be related to the dysregulation of the synaptic protein α-synuclein [1]. It is proposed that PD, PD with dementia (PDD), and DLB represent different manifestations of a continuous disease spectrum of Lewy body disease[1].

Friedrich Heinrich Lewy was the first person to detail the pathological anatomy of PD by personally examining 85 patients [2]. He first described the intraneuronal inclusions, subsequently coined "Lewy bodies" (LBs), in the substantia nigra of PD patients in the early 1900s [3], but he did not attribute an important role to the presence of inclusion bodies for the postmortem diagnosis [4]. The importance of these inclusions, to which Lewy's name was first ascribed by Tretiakoff (Corps de Lewy) in 1919, was seen only after Lewy's death, when LBs began to be considered the defining neuropathological feature of PD. Diffuse Lewy body disease or dementia was identified much later, after the first report of LBs in the cerebral cortex in patients with dementia in 1961 [5]. Ubiquitin and α-synuclein immunocytochemistry in the 1990s allowed easier recognition of LBs [6,7].

The terminology used in the characterization of Lewy body disease (LBD) and clinical syndromes associated with LBD continually evolved. LBD is a term that was proposed in 1984 by Kosaka and colleagues who had been studying the neuropathological changes in patients with dementia for a decade and had examined a series of cases with a combination of LBs in the brainstem, diencephalon, anterior cingulum, amygdala, and cerebral cortex [1]. Kosaka distinguished diffuse LBD with a high LB burden in most areas from brainstem predominant LBD, and transitional LBD that was intermediate between diffuse and brainstem predominant LBD. Clinically, the patients ranged from typical idiopathic PD (IPD) through cases with parkinsonism and dementia, to a few cases with dementia but no extrapyramidal features [8]. Most experts used the term LBD to refer to the histopathological disorder, but other diagnostic terms included diffuse LBD, cortical LBD, LB dementia, and the LB variant of Alzheimer's disease (AD). The overlap in the clinical and pathological terms generated much confusion. Consensus criteria for the clinical and neuropathological diagnoses were published in 1996 by the Consortium on Dementia with Lewy Bodies [9], which suggested that the clinical syndrome should be termed "DLB", and the neuropathological disorder be termed "LBD". Debate continued on how to label patients with typical features of PD subsequently developing dementia. Most authors apply the label DLB to all patients who develop

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parkinsonism after the onset of dementia and also to those who develop dementia within one year from the onset of parkinsonism. The term PDD is referred to those patients who develop dementia more than one year after the onset of parkinsonism. The recent recognition that dementia becomes increasingly prevalent in PD patients followed over the course of the disease, with a prevalence of up to 78% over eight years [10], prompted the generation of evidence-based criteria for PDD. According to these recently published clinical diagnostic criteria, the term PDD should be used to describe dementia that occurs in the context of well-established PD [11]. However, DLB and PDD share many pathological and clinical features and probably represent two clinical entities on a spectrum of LBD, as underpinned by abnormalities in α-synuclein metabolism [12]. A unitary approach to classification may be preferable for molecular and genetic studies and for developing therapeutics, but the one-year rule should remain in place in research studies in which a distinction needs to be made between DLB and PDD [13]. Given the biological similarities between DLB and PDD, yet variability and differences in clinical presentation, the DLB/PDD Working Group recently agreed to endorse the term "Lewy body disorders" as the umbrella term for PD, PDD, and DLB and to use the term "Lewy body dementias" to refer to PDD and DLB [14].

Clinical findings

Neuroepidemiological studies show that DLB, after AD, is the second most common form of degenerative dementia in older people, responsible for 22% of all cases of dementia [15]. A recent systematic review reported that the prevalence of DLB is 0–5% in the general population[16]. DLB usually presents in late adulthood, between the ages of 60 and 90 years, with no significant gender or ethnic differences in prevalence [9]. The disease is a dementing disorder, and progressive and disabling cognitive impairment is the central feature. Patients show a combination of cortical and subcortical cognitive impairments with significant attentional deficits, in addition to executive and visuospatial dysfunctions. Problems with performing sequential tasks, for example using remote controls, moving in familiar surroundings, and ordering from a menu, are typical symptoms [17]. Patients tend to perform poorly on attention, learning, and constructional praxis. In addition to cognitive impairment, the clinical features of DLB include neuropsychiatric features, motor dysfunction, sleep disorders, and autonomic dysfunction.

The diagnosis of DLB is primarily clinical, with no definitive laboratory or diagnostic testing available. The diagnostic criteria for DLB first published in 1996 by the Consortium on DLB were updated in 2005 [13]. The revised criteria divide clinical features into four categories: central, core, suggestive, and supportive.

Central feature

The central feature, essential for a diagnosis of possible or probable DLB, is a dementia defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Early memory loss may be absent, whereas deficits in attention, executive function, and visuospatial ability are especially prominent.

Core feature

Core features include fluctuating cognition, recurrent visual hallucinations, and spontaneous parkinsonism. Fluctuations refer to periods of time when cognition and arousal are

Table 2.1 Consensus criteria for DLB

Central feature (essential for a diagnosis of possible or probable DLB)
Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function; prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression; deficits on tests of attention, executive function, and visuospatial ability may be especially prominent
Core features (two core features are sufficient for a diagnosis of probable DLB, one for possible DLB)
Fluctuating cognition with pronounced variations in attention and alertness
Recurrent visual hallucinations that are typically formed and detailed
Spontaneous features of parkinsonism
Suggestive features (one or more of these in the presence of one or more core features is sufficient for a diagnosis of probable DLB; in the absence of any core features, one or more suggestive features is sufficient for possible DLB)
REM sleep behavior disorder
Severe neuroleptic sensitivity
Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging
Supportive features (commonly present but not proven to have diagnostic specificity)
Repeated falls and syncope
Transient, unexplained loss of consciousness
Severe autonomic dysfunction, e.g. orthostatic hypotension, urinary incontinence
Hallucinations in other modalities
Systematized delusions
Depression
Relative preservation of medial temporal lobe structures on CT/MRI scan
Reduced occipital activity on SPECT/PET perfusion scan
Low-uptake MIBG myocardial scintigraphy
Prominent slow wave activity on EEG with temporal lobe transient sharp waves

Modified from McKeith *et al*, 2005 [13].

clearly abnormal compared with other periods with normal or near-normal functioning [17]. Fluctuations in alertness and attention may last minutes, hours, or days and, when present, are highly suggestive of DLB. The evaluation of cognitive fluctuations may be difficult in the clinical practice. At least one formal measure of fluctuation, such as the Clinician Assessment of Fluctuation scale [18], the One-Day Fluctuation Assessment Scale[18] or the Mayo Fluctuations Composite Scale [19], needs to be used when applying DLB diagnostic criteria. Recurrent, complex, visual hallucinations are generally present early in the course of the disease and remain one of the most useful clinical markers for a diagnosis of DLB. They are present in 33% of patients at the time of presentation and occur at some point in the course of the disease in 46% of cases [12]. In most patients, hallucinations initially occur during nocturnal hours, but over time they tend to occur also during the day independently of the intensity of the ambient light. The perceived images are usually insects, animals, or

people, and these images are so vivid that patients often cannot be convinced that the images are not truly present [17]. Affective responses to the hallucinations vary from indifference to amusement or fear.

Parkinsonism is observed in 75–92% of DLB cases and DLB patients presenting with parkinsonism are, on average, younger than patients presenting with neuropsychiatric features (60 vs. 71 yr) [20,21]. All the manifestations of typical PD may occur, although tremors tend to be more symmetrical and related to posture or action. The severity of extrapyramidal symptoms in DLB is generally similar to that of age-matched PD patients, with or without dementia, with a greater postural instability and gait difficulty in DLB than in non-demented PD patients [22]. As a sign of motor dysfunction, myoclonus may also occur, which may cause confusion with Creutzfeldt–Jakob disease.

Suggestive features

Suggestive features include REM sleep behavior disorder, neuroleptic sensitivity, and low dopamine transporter uptake in basal ganglia. The presence of one or more suggestive features with one or more core features is necessary for a probable diagnosis of DLB. REM sleep behavior disorder (RBD), a parasomnia manifesting by vivid dream enacting behavior, occurs in about 50% of patients with DLB and typically precedes cognitive symptoms by years or even decades [23]. Associated sleep disorders include insomnia, excessive daytime drowsiness, restless legs syndrome, and confusion on waking. Neuroleptic sensitivity to D2-receptor blocking agents is suggestive of DLB and is characterized by the acute onset or exacerbation of parkinsonism and impaired consciousness; however, approximately 50% of patients with DLB receiving typical or atypical antipsychotic drugs do not present this reaction. These agents should never be used as a clinical challenge for diagnosing DLB because of the high morbidity and mortality associated with neuroleptic sensitivity [24].

Supportive features

Supportive features, often present but not proven to be specific for DLB, are autonomic dysfunction, repeated falls and syncope, transient loss of consciousness, non-visual hallucinations, depression, delusions, absence of medial temporal lobe atrophy on CT/MRI scans, abnormal metaiodobenzylguanidine (MIBG) myocardial scintigraphy, and slow wave activity on EEG with temporal lobe transient sharp waves.

Severe autonomic dysfunction may occur early in the disease, featuring orthostatic hypotension, urinary incontinence, constipation, impotence, and swallowing difficulties, and contributing to repeated falls, syncope, and transient losses of consciousness that can be observed in some patients [25]. Falls, often resulting in injury, occur at some point of the disease in 37% of DLB patients [26]. They have been associated with parkinsonism, orthostatic hypotension, vasovagal syncope, and carotid sinus hypersensitivity. Paranoid delusions of persecution, theft, and spousal infidelity occur with some frequency as well and often coexist with hallucinations [27]. Delusions and hallucinations often trigger behavioral problems, leading to profound caregiver distress and precipitating early nursing home admission. Depression is also common in DLB and may appear years before the onset of dementia [27]. Other neuropsychiatric features include anxiety, hallucinations in other sensory modalities (auditory, tactile, and olfactory), aggressivity, agitation, and hypomania.

Overlapping symptoms across the Lewy body disorders

DLB often presents with non-motor symptoms including cognitive impairment, autonomic dysfunction, and psychiatric symptoms. In the early disease stages, this can lead to diagnostic confusion with AD, other autonomic failure syndromes, or primary psychiatric disorders. On the other hand, autonomic and cognitive dysfunctions have been reported for all stages of PD. Constipation may manifest before the classical motor symptoms in about 50% of PD patients[28], and isolated autonomic failure may be the presenting clinical picture of PD [29]. In a prospective study, patients with erectile dysfunction have been reported to have a significantly increased risk of developing PD during the follow-up compared with patients without erectile dysfunction [30]. Bladder and erectile dysfunction, and orthostatic hypotension (OH) may be early findings in PD [31,32], and OH is found in 50% of PDD patients [33].

Cognitive deficits, particularly frontal executive dysfunction and visuospatial deficits, are almost universally identified even in early PD [34]. Community-based studies have suggested that 30–40% of patients with PD will develop clinically defined dementia (PDD). Dementia usually occurs late in the course of PD, an observation proposed by Braak *et al*. [35] that would be in line with the progressive spread of LB pathology from the medulla and olfactory bulb through the pons, midbrain, and basal forebrain, finally to involve cortical areas, but this theory does not account for DLB cases, 25% of which will never show extrapyramidal features, nor does it account for those patients who develop dementia early in the course of PD [1].

By the end stage, DLB and PDD are often clinically indistinguishable with a combination of extrapyramidal features, cognitive impairment, and psychiatric and autonomic dysfunction. In fact, other than temporal differences in the emergence of symptoms, age at onset, and possibly levodopa responsivity, no major differences between DLB and PDD have been found in any variable examined including cognitive profile, attentional impairment, neuropsychiatric features, sleep disorders, autonomic dysfunction, type and severity of parkinsonism, and responsiveness to cholinesterase inhibitors [13]. The previously mentioned studies confirm the overlap between the key syndromes within the spectrum of LB disorders. The presence and distribution of LB may account for clinically distinct syndromes showing various combinations of parkinsonism, dementia, and autonomic failure [36].

Natural history

Definitive information on the prognosis of patients with DLB is not yet available. Some studies show that patients with DLB experience a cognitive decline similar to that in patients with AD [37,38]. Others suggest a worse prognosis for patients with DLB [39]. Symptom progression occurs in both diseases over time, with an average survival of 7.3 years in DLB (vs. 8.5 yr in AD). Women with DLB seem to have a shorter survival time following dementia onset than men with DLB (6.6 vs. 8.1 yr). Patients with DLB have an increased risk of mortality versus patients with AD, possibly owing to the progression of non-cognitive symptoms[38]. Extrapyramidal signs are strong predictors of mortality and long-term care placement, whereas depressive symptoms are important predictors of long-term care placement and survival in nursing homes. Rest tremor seems to be a protective factor in survival analyses, suggesting that tremor-predominant forms of DLB, which are rare, may have a better prognosis than rigid-predominant forms, similarly to the different forms of PD[38].

DLB patients with established parkinsonism have an annual increase in severity, assessed with the unified Parkinson's disease rating scale (UPDRS), of 9%, a rate of progression comparable with PD[40]. Progression, comparably with PD, is more rapid in DLB patients with early parkinsonism (49% increase in the motor UPDRS score in one year).

Among neuropsychiatric symptoms, visual hallucinations were significantly more likely to be persistent in DLB as compared to AD [41]. Delusions and auditory hallucinations, which were more frequent at baseline in DLB than in AD, persisted after one year of follow-up in about 40% of patients with DLB and AD.

Laboratory investigations

There are not yet genotypic, serum, or cerebrospinal fluid (CSF) markers to support a diagnosis of DLB. Studies based on CSF have reported interesting preliminary findings for the combination of amyloid β isoforms as well as α-synuclein, and there are interesting results emerging from studies applying proteomic techniques [42]. These findings deserve further investigations to identify reliable biomarkers for DLB.

Functional imaging of the dopamine transporter by SPECT or PET scans can help in the differential diagnosis of probable DLB and AD. Indeed, striatal dopamine transporter (DAT) uptake is low in DLB, owing to the loss of presynaptic dopaminergic terminals, whereas it is normal in AD. Moreover, imaging of DAT may be useful in diagnostically uncertain cases, as an abnormal scan in a patient with possible DLB is strongly suggestive of DLB, according to the revised criteria [43]. It is important to emphasize that DLB patients can have a highly abnormal DAT uptake even in the absence of signs of parkinsonism. In a recent multi-European phase III trial involving 94 probable DLB and 91 probable AD patients, 123I-FP-CIT SPECT correctly identified 78% of DLB and 93% of AD cases diagnosed according to clinical criteria [44]. A similar accuracy (88% sensitivity, 100% specificity) of 123I-FP-CIT SPECT in the diagnosis of DLB has been reported in prospective studies with neuropathological confirmation (Figure 2.1)[45] .

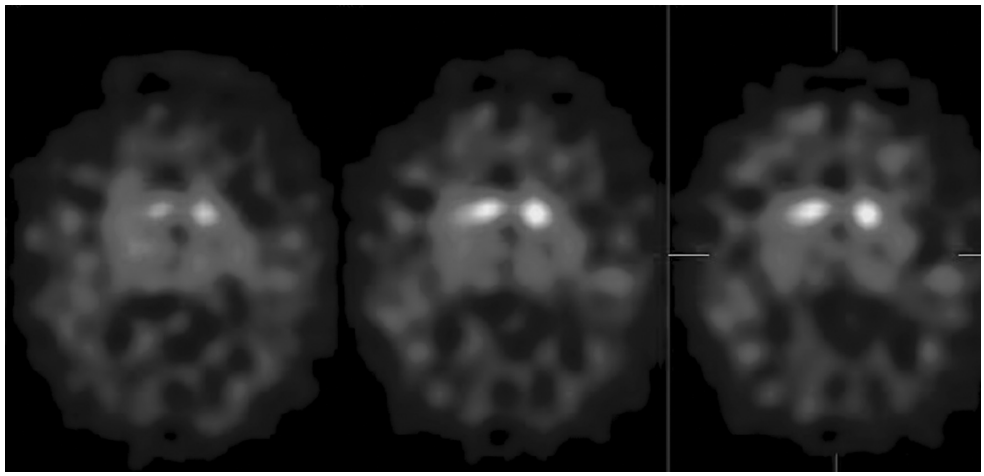

Figure 2.1 Functional imaging of the dopamine transporter by 123I-FP-CIT SPECT showing reduced striatal uptake in a patient affected by dementia with Lewy bodies. (Courtesy: Drs Andrea Varrone and Sabina Pappatà, Institute of Biostructure and Bioimaging, CNR, Naples.) (See color plate section.)

Cardiac scintigraphy with 123I-MIBG provides information on the integrity of the cardiac postganglionic sympathetic neurons. As these autonomic fibers are markedly decreased because of Lewy body-type degeneration in the cardiac plexus, 123I-MIBG scintigraphy shows a low uptake in DLB, irrespective of the presence or absence of clinical autonomic symptoms. This technique seems to have a high accuracy in the differential diagnosis from AD, where there is no such degeneration [46], and in the early identification of DLB from other neurodegenerative diseases with cognitive impairment [47]. In this regard, 123I-MIBG cardiac scintigraphy showed a sensitivity of 94% and a specificity of 96% for the diagnosis of DLB [47]. It is important to be aware that cardiac impairment owing to other etiologies, such as ischemic heart disease, cardiomyopathy, and diabetes, can also damage the post-ganglionic sympathetic neurons, which may give rise to reduced uptake of myocardial 123I-MIBG.

Other imaging techniques can also be helpful. Brain MRI usually shows relative preservation of the hippocampus and medial temporal lobe, a finding that may help to distinguish DLB from AD [48]. Moreover, MRI shows atrophy of the putamen in DLB, but not in AD [49].

Fluorodeoxyglucose (FDG)-PET and SPECT studies using blood flow markers typically show occipital hypometabolism [50,51] and hypoperfusion[52,53] in DLB. Reductions in parietal glucose metabolism and parietal hypoperfusion have also been shown in DLB patients by PET or SPECT studies [53,54]. Generally, FDG-PET metabolic imaging has shown greater ability to differentiate DLB from non-DLB dementia as compared to SPECT perfusion techniques. On the basis of occipital hypometabolism, discriminant analytical techniques applied to group comparative studies have noted sensitivities of 86–92% for DLB with specificities versus 80–92% for AD [51,55]. However, there is limited evidence of the ability of these techniques to categorize individual patients correctly.

The standard EEG is diffusely abnormal in 90% of DLB patients, showing early slowing of the dominant rhythm and transient temporal slow (4–7 Hz) wave activity [56]. Several studies, based on a small number of patients, have shown more slowing of EEG rhythm in DLB than in AD. It is not possible to differentiate DLB and AD on the basis of EEG [57]. However, a recent study showed relevant group differences in EEGs from

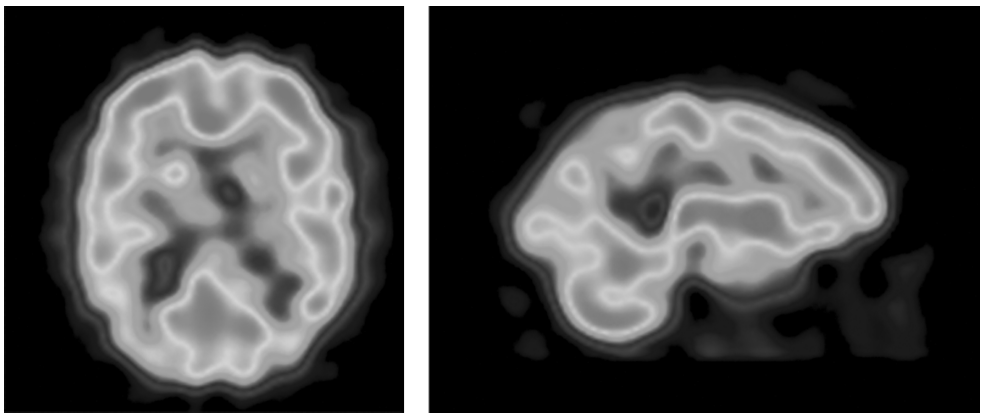

Figure 2.2 FGD-PET showing parietal and occipital hypometabolism in a patient affected by dementia with Lewy bodies. (Courtesy: Drs Andrea Varrone and Sabina Pappatà, Institute of Biostructure and Bioimaging, CNR, Naples.) (See color plate section.)

posterior derivations between AD and DLB patients, both at early stages and two-year follow-up, suggesting that EEG recordings may act to support discrimination between these two disorders at the earliest stages of dementia [58].

Genetics

DLB occurs as a sporadic disease in most cases but a number of familial forms has been reported, suggesting the role of genetics [59,60]. Genetic determinants of DLB are heterogeneous and overlap substantially with those of PD.

Alpha-synuclein (*SNCA*) point mutations [61–63] and whole gene multiplications [64,65] have been associated with clinical and pathological phenotypes ranging from PD to PDD and DLB, highlighting the direct role of α-synuclein overexpression in the pathogenesis of the spectrum of Lewy body disorders. Furthermore, it appears to be a dose effect, with *SNCA* duplications more often associated with classic PD[66,67] and *SNCA* triplications more often responsible for PDD and DLB [64,65]. The type of missense mutations might also be critical for the resulting phenotype; in fact the missense mutation A30P is found in association with typical PD [68], whereas E46K and A53T are associated with the entire range of Lewy body disorders [61–63,69]. Alpha-synuclein is a member of a family of presynaptic proteins that includes β- and γ-synuclein. There is evidence that β-synuclein might protect against α-synuclein aggregation [70]; therefore, β-synuclein (*SNCB*) mutations might be responsible for LB disorders. Although *SNCB* mutations have not been identified in PD patients, two missense mutations (V70M and P123H) have been identified recently in two unrelated DLB index cases [71]. The two mutant β-synuclein proteins have been found to enhance lysosomal pathology in a cell model of synucleinopathy, supporting a causative role for the mutated variants in inducing neurodegeneration [72].

Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene have been identified in familial parkinsonism [73,74]. To date, a wide clinical–pathological spectrum is associated with *LRRK2* mutations, which would seem to include clinically and pathologically defined DLB [74,75].

Mutations in the glucocerebrosidase (GBA) gene have been reported in association with parkinsonism and LB pathology among Gaucher's disease patients and their relatives [76–78]. An association between *GBA* missense mutations and PD has been detected among Ashkenazi Jews [79,80]. More recently, a high prevalence of *GBA* mutations was reported among patients with pathologically defined DLB [81]. In a case-control study, the frequency of *GBA* mutations was similar in PD (2.9%) and DLB (3.5%) and significantly higher than the control (0.4%), suggesting a modest population-attributable risk for *GBA* mutations in Lewy body disorders [82]. Further studies are required to better understand the role of *GBA* in Lewy body disorders.

Recently, a novel locus for a familial, autosomal dominant DLB has been identified on the long arm of chromosome 2 (2q35-q36; logarithm of odds score of 3.01) in a large Belgian family [83]. Interestingly, this locus for DLB overlaps with *PARK11*, a locus previously identified in families with autosomal dominant PD [84].

In conclusion, genes involved in genetic forms of PD (*SNCA*, *LRRK2*, and *GBA*) account for most familial DLB cases. Nevertheless, these genes explain only a minority of cases and the discovery of further genes for Lewy body disorders remains a key research priority.

Pathology

Alpha-synuclein represents the common biochemical substrate of pathology in IPD, PDD, and DLB [85]. Lewy-related pathology includes LB and Lewy neurites (LNs), which are defined as α-synuclein-positive inclusions in the neuronal cell body and the dendrites and axons, respectively. Alpha-synuclein-positive inclusions have also been found in the presynaptic terminals [86] and the glia [87,88].

There are few neuropathological studies directly comparing the three diseases. In PD, LBs and LNs are located mainly in the substantia nigra and other brainstem nuclei such as the locus ceruleus and raphe [89], whereas in DLB, Lewy-related pathology is present in both the brainstem and in a number of cortical areas [90,91]. In PDD, diffuse cortical LBs are the main substrate of dementia [91,92]. Furthermore, senile plaques and neurofibrillay tangles, a hallmark of AD pathology, are common pathological features in both PDD and DLB [91,92]. Some studies have suggested that patients with DLB have more cortical LB load and more brain atrophy compared with PDD patients [93,94]. A more comprehensive report has confirmed greater cortical LB pathology and more senile plaques in DLB versus PDD and has shown that neurofibrillary tangles were rare in both diseases [95].

According to the revised consensus criteria [13], two major aspects have to be considered in the pathological features of DLB. First, because the pattern of regional involvement is more important than total LB count, DLB cases are divided into brainstem predominant, limbic/transitional, and diffuse neocortical subtypes. Secondly, based on the evidence of the significant concurrent AD pathology [96], it has to be taken into account that "a DLB clinical syndrome is directly related to the severity of Lewy-related pathology and inversely related to the severity of concurrent AD-related pathology" [13].

To date, the complex interaction between LB and AD pathology remains unclear. Some studies have suggested that the process of LB formations is triggered, at least in part, by AD pathology [97,98]. Others have reported that amyloid rather then tau enhances α-synuclein pathology [99]. These intriguing interactions might represent the biomolecular mechanisms underlying the overlapping pathology of DLB and AD [100].

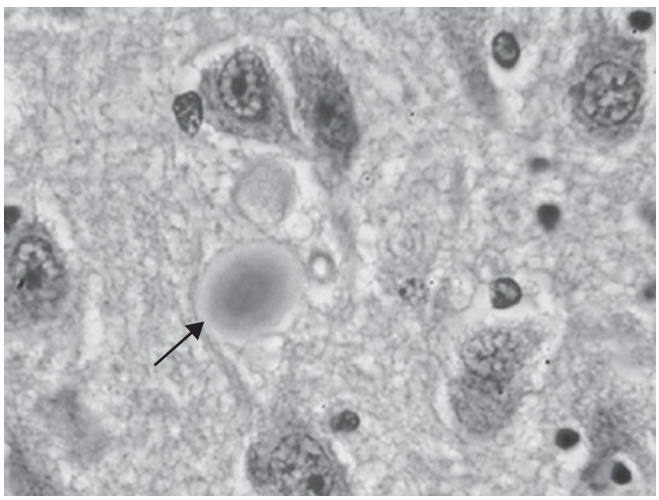

Figure 2.3 Brain cells containing a Lewy body (arrow) (hematoxylin-eosin staining; high-power magnification). (Courtesy: National Human Genome Research Institute.)

Neuropathological studies have tried to determine whether PDD and DLB are distinct entities or part of a continuum. There is a clear relationship between PDD and DLB with a gradation of neuropathological and neurochemical characteristics across a spectrum spanning from late PDD (parkinsonism for >9.5 years prior to dementia) to early PDD (parkinsonism for <9.5 years prior to dementia) and DLB [101]. In particular, a correlation has been found between a longer duration of parkinsonism prior to dementia and less severe cortical LB pathology and fewer senile plaques. The progressive spread of Lewy body pathology as proposed by Braak,*et al.* [35], beginning from the medulla and olfactory bulb and advancing through the pons, midbrain, and limbic structures to finally involve the neocortex, is compatible with the observation that dementia usually occurs late in the course of PD. However, this model does not seem applicable for DLB, which starts in the amygdala, advances to the limbic cortex, and finally spreads to the neocortex [102], suggesting that the site of the initial lesions differs in the two diseases.

This apparent inconsistency might be explained by the exclusion of DLB patients in the original Braak analysis [1][14]. Alternatively, it has been proposed that distinct patterns of Lewy-related pathology in PDD and DLB may reflect the regional differences in both dysfunctional neurons and increased expression of α-synuclein protein [103], rather than a caudal-to-rostral-wide spread over the course of the time [104]. This view is supported by the uncertain pathophysiological significance of LBs. The Braak scheme assumes that Lewy pathology reliably identifies dysfunctional neurons, but the assumption that α-synuclein immunopathology detects where PD begins is now debated [104]. In fact, intraneuronal increase of α-synuclein has been identified in several injury models and has been proposed to play a protective role [105–107].

Based on this growing body of evidence, a critical re-evaluation of the Braak staging model is needed to account for the different pathological patterns observed across the Lewy body disorders spectrum.

Management

To date, no therapy altering α-synuclein pathophysiology has been identified. Although α-synuclein-positive LBs are the prominent pathological change in PD, PDD, and DLB, there is a suggestion that amyloid, tau, and α-synuclein pathology may be synergistic, raising the possibility that treatments aimed to affect these abnormal proteins in one disease may be helpful in others as well [108]. On the other hand, there is a symptomatic therapy for the various clinical manifestations of LB disorders. Clinical management includes early detection, diagnosis, and treatment of cognitive impairment; assessment and management of neuropsychiatric and behavioral symptoms; treatment of movement disorder; and management of autonomic dysfunction and sleep disorders [109].

Treatment of cognitive impairment

Cognitive and functional abilities can improve with cholinesterase inhibitor therapy in both PDD and DLB. The cholinesterase inhibitors used most often in clinical practice include donepezil, rivastigmine, and galantamine. Rivastigmine is the only drug in this class that has been proven to be effective and safe in DLB in a double-blind placebo controlled trial [110], but open trials on small series have also suggested some efficacy of other cholinesterase inhibitors.

Until not long ago, most published trials in PDD had an open label design[111,112], except some double-blind studies on donepezil in small series of PDD patients [10,113,114].

Recently, a large placebo-controlled trial of rivastigmine has reported significant improvement of cognition in PDD [115]. This improvement appeared to be sustained in patients who were able to tolerate an open-label extension [116]. Memantine seems to worsen cognitive and neuropsychiatric symptoms in DLB patients, as reported in a few cases [117,118].

Treatment of neuropsychiatric features

Visual hallucinations are often the most troubling neuropsychiatric feature in DLB and PDD, but they do not always require drug treatment. Cholinesterase inhibitors and atypical antipsychotics can be considered for management of hallucinations, delusions, and apathy [110,119–122]. The preferred atypical antipsychotics are clozapine [123–125] and quetiapine [124,126]. Because neuroleptic sensitivity can occur in DLB patients with exposure to even small doses of typical neuroleptics, these agents are strongly discouraged now [127].

Depression is very common in DLB and PDD and sometimes requires treatment. To date, there have been no systematic studies of antidepressive drugs in DLB and PDD depression. However, SSRIs (selective serotonin reuptake inhibitors) and SNRIs (selective noradrenaline [norepinephrine] re-uptake inhibitors) represent the preferred pharmacological treatment. In fact, the anticholinergic effects of tricyclic antidepressants and paroxetine make these drugs unattractive in the treatment of DLB and PDD.

Treatment of motor dysfunction

Because motor impairment is significant in patients with PDD and in some patients with DLB, studies aimed to treat parkinsonism are relevant. One study has shown that patients with PDD and DLB respond to dopaminergic therapy to a lesser degree than patients without dementia [128].

Recently, L-dopa has been shown to be well-tolerated in most DLB patients, but only a third of them experienced significant improvement in parkinsonism [129]. Cognitive functions and neuropsychiatric symptoms were not adversely affected by L-dopa treatment in an open-label study in a small sample of DLB patients [130].

Treatment of other symptoms

Orthostatic hypotension is a crucial and disturbing symptom in patients with LB disorders. Elevating the head of the bed to avoid pressure natriuresis; increasing fluid intake as well as salt in the diet; and using salt tablets, thigh-high compression stockings, fludrocortisone, and midodrine are all potential treatments for OH.

REM sleep behavior disorder is common among patients with Lewy body disorder and responds to clonazepam, usually effective at 0.25–1.0 mg/night[131,132]; to melatonin, usually effective at 3–12 mg/night, either as monotherapy or in association with clonazepam [133]; or to quetiapine, usually effective at 25–100 mg/night [131][132].

Conclusions

The relationship between PDD and DLB is still a matter of intense discussion and debate. Two models have been proposed to explain the link between PDD and LBD: a model whereby there is a PDD–DLB continuum the boundaries of which are related to the time interval between the onset of cognitive respect to motor symptoms, and a model where PDD

and DLB are defined as discrete entities [13]. The concept that these two disorders have to be viewed as a single entity (α-synucleinopathy) is preferable in order to better research and understand biological and pathophysiological mechanisms and to develop treatment strategies [14]. The genetic determinants of DLB and PDD as well as PD, including alterations in *SNCA* and *LRRK2* and certainly other genes, will offer further insights into the pathogenesis [17]. Clinical research will help to detect early markers of disease; to better define its natural history; and to develop cognitive and non-cognitive measures, which will be useful in the setting of PDD/DLB. The obvious hope is that disease modifying or preventing agents can be developed in the near future.

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