Parkinson's disease dementia and dementia with Lewy bodies – epidemiology, risk factors and biomarkers

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ABSTRACT

Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) are common and debilitating dementia syndromes accompanied by Parkinsonism and a range of other psychiatric, sleep and autonomic disturbances. Disease mechanisms are unknown, but aggregated Lewy bodies containing alpha-synuclein are believed to play a central role in the pathogenesis. Point-prevalence of dementia in Parkinson's disease (PD) is approximately 30%, and the majority develop dementia as the disease progresses. Recent studies suggest that 25-30% of non-demented PD patients have mild cognitive impairment (MCI), and 15-20% already have it at the time of the diagnosis. PD-MCI is a strong predictor of PDD. There are few well-designed epidemiological studies of DLB, but available evidence suggests that 15-20% of the total dementia population have DLB. Predicting future cognitive impairment is a priority, but the pre-dementia stage of DLB is essentially unexplored. Promising biomarkers are being researched, but, given the complexity of this disease, a multimodal approach is more likely to permit diagnostic precision in the future.

INTRODUCTION

James Parkinson's "essay on the shaking palsy" written in 1817, was the first clinical description of a patient group characterized by motor symptoms such as slowing of movement, tremor and flexed posture (1). Almost a hundred years later Friedrich Lewy discovered that abnormal aggregates of intracytoplasmatic proteins could be found in the brainstem of Parkinson's disease (PD) patients, now known under the eponym of Lewy bodies. Lewy bodies in the substantia nigra are now regarded as the hallmark of idiopathic PD, but the underlying mechanisms are still unknown. Although Friedrich Lewy described significant cognitive impairment in PD patients, he did not connect this important observation to protein aggregation and development of dementia, and for decades PD was still regarded as a disease with pure motor dysfunction. From 1960 and later more sensitive immunocytochemical methods could detect Lewy bodies also in cortical and limbic structures in patients with dementia both with and without typical motor symptoms. Similar histopathological changes were also seen in the peripheral nervous system raising awareness of a disease group with a diversity of symptoms affecting several transmitter systems (2,3). Together with the remarkable efficacy of dopaminergic drugs in the treatment of motor symptoms, these important findings initiated an increased interest in cognitive impairment and other non-motor features in PD and related disorders. The recent detection of alpha-synuclein as the main constituent of Lewy bodies was another breakthrough (4).

A new distinct dementia subtype emerged with alpha-synuclein containing Lewy bodies as the defining hallmark. The clinical phenotype and histopathology were different from that of vascular dementia and Alzheimer disease, and thus the first clinical criteria for dementia with Lewy bodies (DLB) and clinical, diagnostic criteria for dementia associated with PD (PDD) were proposed in 1996 and 2007 respectively (5,6). There has been much debate as to whether these two disorders are different, but the common view now is that the similarities dominate, and that the relative timing of dementia and motor symptoms is the major difference. Lewy body disease has thus been proposed as an umbrella term for PD, PDD and DLB (7).

In this review we will attempt to address the important feature of cognitive impairment in Lewy body disease. Despite similarities between DLB and PDD, we will describe the current known risk factors and epidemiology separately. We will review the current status of both established and potential future biomarkers, such as clinical features, genetics, cerebrospinal fluid (CSF) and imaging parameters.

THE PREVALENCE AND INCIDENCE OF DLB

DLB is defined by the presence of dementia together with two of three core symptoms: (1) Parkinsonism, (2) typically well-formed and persistent visual hallucinations and (3) fluctuating cognition and/or consciousness (5). According to the revised clinical diagnostic criteria from 2005, a probable DLB diagnosis can be made with only one core symptom together with one

Table 1. Community-based studies reporting the frequency of dementia with Lewy bodies (DLB).

Reference	N	Criteria*	Age	Frequency	Comment
(MRC-CFAS, 2001)****	109	P	>70	12%	MRC-CFAS study, UK
(Yamada, 2001)	142	1	≥65	0.1%	Rural town, Japan
(Miech, 2002)	185	0	≥65	3.2%	Cache County Study, US
(Herrera, 2002)	118	1	≥65	1.7%	Brazil
(Shaji, 2002)	51	1	>60	12%	Kerala, India
(Stevens, 2002)	107	1	≥65	30.5%	Only patients with VH[1] included
(de Silva, 2003)	28	1	≥65	3.6%	Semi-urban population, India
(Harvey, 2003)	227	CC	<65	7%	Age below 65 years, UK
(Wakisaka, 2003)	102***	P	>65	41.4%	Community based pathology study, Japan
(Lopez, 2003)	707	1	>65	3.5%	US Cardiovascular Health Cognition Study
(Rahkonen, 2003)	137	1	≥75	21.9%	Persons aged 75 or older in Finland
(Sambrook, 2004)	766	1	>60	3%	Canadian Outcomes Study in Dementia
(Lam, 2008)	2073	1	>70	3.6%**	Thematic Household Study, Hong Kong
(de Pedro-Cuesta, 2009)	1194	0	>70	0.8-2%	Reanalysis of Spanish community surveys
(Matsui, 2009)	275	P	≥65	10.6%	Pathologically verified diagnoses Japan

Notes: *Criteria 1 = McKeith et al. 1996, 0 = no criteria, CC = clinical criteria, P=pathological. **DLB+Parkinson's disease dementia (PDD) ***29 demented ****("Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS)", 2001)

[1] Visual hallucinations

or more suggestive features like REM sleep Behavior Disorder (RBD), neuroleptic hypersensitivity or a pathological single photon emission computed tomography (SPECT) using an ioflupane (^{123}I) biomarker (DaTSCAN) (8). A diagnosis of possible DLB can be made with only one core or suggestive feature. In addition, the consensus criteria list a number of supporting clinical features like frequent falls, psychotic and depressive symptoms and autonomic failure. The revised clinical criteria awaits further systematic validation, but the sensitivity and specificity has been found to increase if RBD is added as a core feature (sensitivity 90%) and cognitive fluctuation excluded (specificity 85%) in advanced disease (9).

Few community-based epidemiological studies have focused on DLB and few have applied the clinical diagnostic criteria (table 1). In a review of epidemiological studies Zaccai and her colleagues concluded that the prevalence of DLB ranges from 0 to 5% with regard to the general population and from 0 to 30.5% of all dementia cases. A large part of this variation is probably due to methodological differences (10). Symptoms such as fluctuation are hard to identify clinically if not specifically investigated, and instruments like the Mayo Fluctuations Scale and the Clinician Fluctuation Inventory are recommended as screening instruments for this purpose (11,12). The same holds true regarding the RBD, and therefore, the Mayo Sleep Questionnaire is recommended to screen for sleep disorders in dementia in clinical settings (13).

Among the most systematic studies are the Islington study from Britain, the Kuopio study from Finland and a community-based survey from Japan. This population-based Hisayama Study found DLB in 10.6% of neuropathologically confirmed dementia cases and pure DLB was confirmed neuropathologically in 4.4% (14). The British Islington Community Study of Dementia in North London included 107 patients with dementia. It found 9.7% with a clinical diagnosis of probable DLB, while 30.5% had combined possible or probable DLB (15). A health survey in the Kuopio area in Finland of people aged 75 years or older found the proportion of DLB to be 21.9% of all dementia cases (16). These three studies provide the best estimates of the prevalence of DLB in the general population and suggest that DLB accounts for 10-22% of dementia cases in the 65 years or older age group, indicating that about 1% of the population over 65 years may suffer from DLB. In the DemVest study in Western Norway we applied the revised consensus criteria on a referral cohort to old age psychiatry and geriatric medicine clinics, including all referrals with a first time diagnosis of mild dementia (defined as a Mini Mental State Examination (MMSE) score of 20 or more). In our study, 15.8% of persons with mild dementia were diagnosed with probable DLB and 20% with possible and probable DLB combined with other symptoms (17). Only four incidence studies exist and report the incidence of DLB from 0.7 to 1.4 new cases for every 1,000 persons per year (14,18-20) (table 2).

RISK FACTORS FOR DEVELOPING DLB

Very few studies have explored the early, pre-dementia stages of DLB, but evidence is emerging to suggest that several possible starting points and trajectories can lead to the pathological and clinical syndrome of DLB (Figure 1).

Table 2. Studies reporting the incidence of dementia with Lewy bodies (DLB).

Study	Age	N*	DLB incidence
(Matsui et al., 2009) Hisayama-study	65+	828/81	1.4 per 1000 persons per year
(de Lau et al., 2004)	55+	6839[1]	0.7 per 1000 persons per year (95% CI 0.4-1.0)
(Lopez-Pousa et al., 2004)	75+	1198/18	2% of annual clinical dementia incidence in a memory clinic.
(Miech et al., 2002)	65+	185/6	0.1% per year in general population. 3.2% per year of all new dementia

*Total population/DLB

[1] DLB is not diagnosed by strict use of the diagnostic criteria, but the authors have made the assumption that subjects with Parkinsonism associated with dementia (numbering 26) all had DLB.
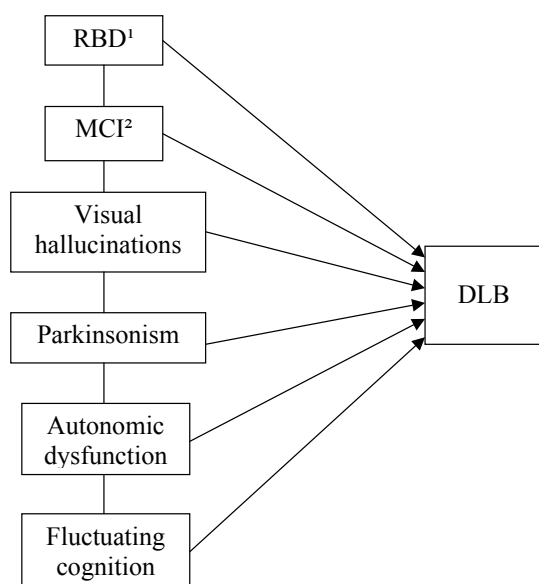

Figure 1. Potential presenting symptoms in DLB.

[1] REM sleep behavior disorder
[2] Mild cognitive impairment

Genetic contributions

Most DLB cases occur sporadically, although families have been described as having several members diagnosed with DLB with gene alterations in different locations, some of which overlap with PD and others with AD. Cousins of DLB patients have a 2.3 fold increased risk of developing DLB compared to members of the general population (21). Traditional genetic studies have identified multiplications (22,23) and mutations in the gene encoding alpha-synuclein (24-26) and beta-synuclein (27). Genetic mutations known to be risk factors of early onset familial Alzheimer's disease, like PSEN 1 and PSEN 2, have also been identified in DLB (28).

The APOE ε4 allele is the strongest genetic risk factor for developing AD, but in DLB there are conflicting results regarding APOE as a risk factor (29). Genome-wide association studies (GWAS) have not yet been presented for DLB but it is to be hoped that in the near future more of the underlying disease mechanism and risk factors will be revealed.

Clinical features preceding DLB

Mild cognitive impairment (MCI) has been shown to precede Alzheimer dementia (AD) with an annual conversion rate of about 10-15% (30), but the MCI stage of DLB is undefined and essentially unexplored. A clinicopathological study of eight MCI patients with subsequent autopsy-proven Lewy body disease shoved that RBD preceded MCI in six cases with a median of 12 years (31). The cognitive domains most frequently affected at the pre-dementia stage were attention, executive and visuospatial functioning. Memory was less frequently impaired. The same cognitive pattern was seen in another study with a similar design (32). Parkinsonism, visual hallucinations and delirium were shown to be early features compared to the MCI-stage of Alzheimer's disease, which is dominated by memory problems. In a retrospective study of 61 mildly demented DLB patients, carers reported visual hallucinations and memory impairment as the most frequent presenting symptoms, suggesting mixed and overlapping symptoms with AD-MCI (33). In another autopsy-proven study, visual hallucinations were seen as the best positive predictor and the absence of visuospatial impairment the best negative predictor of a later diagnosis of DLB versus AD (34).

In the DemVest study we found higher frequencies of RBD and Excessive Daytime Sleepiness (EDS) in mild DLB compared to normal controls and mild AD patients. RBD started on average seven years (range 0.5-35 years) before dementia was diagnosed in 39 persons, indicating a strong association (unpublished data from the DemVest study). This long-duration pre-clinical phase was also demonstrated in another study (35). In a recent study RBD conferred a 2.2-fold increased risk of developing PD-MCI over four years (36).

Pure Autonomic Failure (PAF) is restricted clinically to the peripheral nervous system and includes orthostatic hypotension, constipation, olfactory dysfunction and urinary incontinence. PAF has been shown to be the initial presentation in both DLB and Parkinson's disease (37), and a positive DaTSCAN in PAF supports the hypothesis of a common etiology (38).

POTENTIAL BIOMARKERS IN DLB

Due to the relatively low sensitivity of the consensus criteria for DLB, the need for reliable biomarkers is evident. A complicating factor is the heterogeneous brain pathology in DLB and the considerable overlap between neuropathological changes and clinical presentation in DLB and AD.

Among established biomarkers for AD are atrophy of the medial temporal lobe (hippocampus), a low concentration of beta-amyloid and a high concentration of total-tau and phospho-tau in the CSF (39,40). These patterns can also be seen in DLB, but typically the hippocampus is less damaged and the CSF changes less clear in comparison with AD (41), and it cannot be used to separate DLB from AD on an individual level.

Reduced levels of alpha-synuclein in the CSF of DLB patients compared to that of those with AD have recently been demonstrated (42), but the studies are small and routine measurement of alpha-synuclein has proven technically difficult. At present, more confirmatory studies are needed in order to incorporate alpha-synuclein as a good and valid biomarker for DLB.

Slowing of the EEG rhythm is a frequent finding in AD and other dementias, but several studies have shown a more pronounced slowing in DLB patients (43). These studies have, however, included few patients, and larger studies have shown conflicting results (43). In addition, none of the published studies report information about diagnostic sensitivity and specificity, and thus EEG findings cannot serve as a reliable biomarker for DLB.

Autonomic dysfunction involving the cardiovascular system is common in DLB and myocardial scintigraphy with ^{123}I-metaiodobenzylguanidine (MIBG) enables the quantification of post-ganglionic cardiac sympathetic innervation. Several studies have demonstrated reduced cardiac uptake in DLB compared to AD patients (43), but larger multicentre studies are lacking and more conclusive evidence is pending.

Radiolabelled tracers used in SPECT can measure regional, cortical blood flow and show a typical pattern of reduced perfusion in temporoparietal areas in AD. In DLB a pattern of occipital and parietal hypoperfusion is more common, often referred to as the "horse-shoe sign". Similar findings have been found for fluorodeoxyglucose-positron emission tomography (FDG-PET) (44). Relatively few studies with small samples have assessed the precision of cerebral SPECT as a biomarker for DLB (43), and the available results are conflicting, indicating the need for multicentre studies for better diagnostic accuracy.

The most convincing evidence exists for ioflupane (^{123}I) SPECT (DaTSCAN), where radiolabelled ioflupane binds to the dopamine transporter in the striatum. In cases of reduction of dopaminergic neurons in the substantia nigra, the visualization of dopamine transporters is greatly reduced. These findings were first demonstrated in PD, but can now also be seen in pre-clinical cases of nigro-striatal degeneration including multiple system atrophy, progressive supranuclear palsy and DLB. This means that DLB patients without clinically detectable Parkinsonism can now be identified (45), whereas the scans of patients with AD are normal. In a large pivotal multicentre study, DaTSCAN demonstrated a sensitivity of 78% and a specificity of 90% in distinguishing probable DLB from AD (46).

Recent findings suggest that DaTSCAN could be of even greater clinical relevance in identifying patients with possible DLB. In a 12-month longitudinal study no patients with possible DLB and a normal scan at baseline had developed probable DLB at the follow-up examination. In contrast, 63% (12 of 19) of subjects with an abnormal scan had probable DLB at follow-up, a significant difference (47). Thus, DaTSCAN can help to identify DLB at an early stage, before the full clinical syndrome has developed.

THE PREVALENCE AND INCIDENCE OF PDD

PDD is common, and the prevalence is estimated to be about 5% of all cases of dementia (17). Cognitive impairment in PD has recently been reviewed in detail (48).

Several cross-sectional epidemiological studies have reported that the proportion of PD patients who have dementia is approximately 30% (49,50). Cross-sectional studies, however, underestimate the proportion of people with dementia, since mortality in PD is influenced by dementia. Longitudinal studies have reported a six times higher risk of developing dementia in PD compared to people without PD of the same age. The incidence of dementia in cross-sectional PD cohorts is 100 per 100,000 patient-years. Consequently, a very high cumulative proportion of up to 80% with dementia has been reported among PD patients (51,52). A lower incidence has been reported for the first years after diagnosis. In a longitudinal study based on an incidence PD-cohort, a dementia incidence of 30 per 100,000 person-years was reported (53) and slightly less than 50% of the cohort had developed dementia eight years after the diagnosis. The mean time-period to diagnosis with dementia was 6.2 years.

Variations in the course of cognitive impairment

There is a wide variation in the time from onset of PD to dementia. Whereas some patients develop dementia within a few years of the diagnosis, others do not show signs of dementia for more than 20 years (54). The mean rate of cognitive decline in PD is approximately 1 point per annum on the MMSE (55), but for unknown reasons there is large inter- and intra-individual variation in the rate of decline. As reported above, a slower rate of decline occurs in the early stages of the disease. Typically, in an individual PD patient, a period of no or very little decline is followed by an inflexion point after which a much more rapid decline occurs, with large inter-individual variation in the time-period to

this inflexion point (56,57). After the onset of PDD, the progression to the terminal stage of the illness is less variable, and there is an average of 3 years with increasing disability leading to death, whatever the age of onset (58). Identifying predictors of time to diagnosis of dementia and of the rate of cognitive decline is thus a key clinical and research priority.

RISK FACTORS FOR EARLY COGNITIVE DECLINE IN PD

A shorter time to cognitive impairment is associated with older age at diagnosis of PD, non-tremor dominant motor subtypes with significant postural instability and gait disturbances (53,59). In addition, visual hallucinations, RBD (36,60) and olfactory dysfunction (61) are associated with a shorter time to the development of dementia.

Genetic contributions to cognitive impairment in PD

Several studies have reported a familial association between dementia and PD, suggesting that genetic factors influence the emergence of cognitive impairment and dementia in PD (62). Despite the progress in identifying genes that cause or increase the risk of PD, the specific genetic contribution to cognitive impairment in PD is not known.

The H1 and H1p haplotypes of the microtubule-associated protein tau (MAPT) have been found to be significantly associated with dementia with significant odds ratios ranging from 1.35 to 3.7 (63,64), although not consistently. Alpha-synuclein gene duplications may lead to cognitive impairments and dementia (65). PD patients with glucocerebrosidase (GBA) mutations have more frequent and severe cognitive impairments when compared to sporadic cases of PD (66), and glucocerebrosidase (GBA) mutation status may be an independent risk factor for cognitive impairment in patients with PD (67).

Other typical PD mutations such as LRRK2 and Parkin-mutations do not seem to be associated with the development of cognitive impairment (68). Mutations of the COMT gene are associated with dopamine-related cognitive deficits, such as reduced attention, but do not seem be associated with increased risk of dementia (69). Finally, inconsistent results have been found regarding the associations between APOE genotype and butyrylcholinesterase-K genotypes and the risk of dementia (70-72).

Mild cognitive impairment

About 20-25% of PD patients without dementia have mild cognitive impairment (PD-MCI) (73). It is noteworthy that, even at the time of diagnosis, MCI is observed in 15-20% of people with PD, even in non-treated patients (74). Recently the Movement Disorders Society commissioned a task force (MDS-TF) which proposed the first clinical consensus criteria for MCI in PD (75). Importantly, the early cognitive changes in PD seem to predict subsequent development of de-

mentia. The cognitive profile in PD is heterogeneous, and it has recently been demonstrated that impairments of visuospatial functions and memory occur in addition to the well-known attentional and executive deficits (76). Some evidence exists that semantic memory and visuospatial dysfunction, but not executive impairment, predict progression to dementia in PD patients (69). One interpretation of these findings is that frontal-type deficits are more related to dopaminergic lesions (causing more mild cognitive deficits), whereas the more posterior cognitive deficits may be associated with structural pathologies such as temporo-parietal Lewy bodies and plaque pathology (giving more rapid decline and dementia). Further studies are needed to test this hypothesis.

BIOMARKERS PREDICTING COGNITIVE DECLINE IN PD

Several different biomarkers have been associated with cognitive impairment in PD, and recently several longitudinal studies have been reported (77-81). However, larger multicentre studies with robust and a priori defined cut-off points are necessary before these markers can be implemented in clinical practice.

Structural imaging

Most studies have used structural magnetic resonance imaging (MRI) and shown that atrophy of the parietal-temporal lobe, entorhinal cortex, hippocampus, prefrontal cortex and posterior cingulate cortex (82-86) are associated with PDD. Similar, but less marked, changes have also been identified in PD-MCI (85,87). An AD-like pattern of atrophy (hippocampus, parietal-temporal cortex) was recently found to be related to cognitive performance in PD and it was suggested that these changes might be used to predict a global cognitive decline in non-demented patients over a 2-year follow-up period (88).

EEG

Quantitative electroencephalography (QEEG) studies suggest that low-frequency content is associated with cognitive impairment in PD, and that QEEG measures could also predict the risk of developing dementia in the future (77).

PET

Reduced glucose metabolism in both frontal and parietal cortex measured by FDG-PET has been found to be associated with cognitive decline in PD-MCI (89). More specifically, hypometabolism in the temporal cortex has been associated with verbal memory, in the frontal cortex with executive dysfunction and in the parietal cortices with visuospatial dysfunction (90). A recent longitudinal study suggested that early metabolic changes in visual association and posterior cingulate cortices could predict incident dementia in PD (81).

Perfusion SPECT

Cross-sectional studies using SPECT have reported hypoperfusion in lateral parietal and frontal cortex in

PD patients without dementia, which correlated with cognitive impairment (91). Bilateral hypoperfusion in posterior parietal lobes and in the right occipital lobe were seen in PD-MCI, which differed from the pattern seen in non-PD-MCI (92). Perfusion has also been shown to aid in the prediction of cognitive decline in PD (80).

CSF

It has been reported that beta-amyloid (1-42) levels were lower and total-tau and p-tau were higher or normal in PDD patients when compared to PD patients without dementia and controls (93). Likewise, a prospective study indicated that lower baseline CSF beta-amyloid (1-42), but not total-tau and p-tau (181p), was associated with more rapid cognitive decline (78). Detailed analyses of several splice variants of beta-amyloid showed that early PD patients displayed significant reductions not only of CSF Aβ42, but also Aβ40 and Aβ38. These reductions were associated with memory impairment, but not with executive-attentional or visuospatial dysfunction (94). These observations suggest that amyloid pathology contributes to cognitive impairment in PD.

Patients with PD and DLB have shown lower monomeric CSF alpha-synuclein levels than patients with AD and controls (95). Correlations between cognitive status and lower CSF alpha-synuclein have been reported in DLB (42), but at present not in PD. Alpha-synuclein oligomers or phospho-alpha-synuclein (129p) in CSF has also been reported to be higher in patients with PD compared to patients with AD or controls (96).

FINAL REMARKS – CONCLUSION

Both DLB and PDD are common and highly debilitating syndromes with a variety of symptoms. The overall negative impact on the individual patient and the carer, as well as the health-related costs of Lewy body dementia are even higher than those of AD (97-99). Although the full clinical syndrome seen in DLB can occur also in PD, PD preceding dementia should be diagnosed as PDD rather than DLB.

Early disease detection is a priority in order to give patients and carers an explanation of the diversity of symptoms and to provide targeted medication and care.

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