Prodromal dementia with Lewy bodies

P. C. Donaghy1*, J. T. O’Brien2 and A. J. Thomas1

1 Institute for Ageing and Health, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, UK
2 Department of Psychiatry, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK

Background. The clinical condition of dementia is now recognized as a diagnosis that can only be applied too late in the disease process to be useful for therapeutic approaches centring on disease modification. As a result, in recent years increasing attention has been given to mild cognitive impairment (MCI) and the diagnosis of prodromal dementia. This paper reviews the evidence for the clinical presentation of prodromal dementia with Lewy bodies (DLB).

Method. A Medline search was carried out to identify articles with original data on the prodromal presentation of DLB.

Results. In MCI cohorts that progress to dementia, the proportion diagnosed with DLB is similar to that reported in dementia cohorts. Prodromal DLB may present as any MCI subtype, although visuospatial and executive domains may be most commonly affected. Rapid eye movement (REM) sleep behaviour disorder (RBD), autonomic symptoms, hyposmia, hallucinations and motor symptoms seem to be more common in prodromal DLB than in prodromal Alzheimer’s disease (AD). Some of these symptoms can precede the diagnosis of DLB by several years. There has been little research into the use of biomarkers in prodromal DLB, although in RBD cohorts, clinical and imaging biomarkers have been associated with the development of DLB.

Conclusions. The evidence available suggests that prodromal DLB may be differentiated from other dementia prodromes in most cases. Further research is needed to confirm this, and to assess the utility of biomarkers such as [123I]-FP-CIT and [123I]-MIBG imaging.

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Introduction

The clinical condition of dementia, by definition a global cognitive decline with functional impairment, is now recognized as a diagnosis that can only be applied too late in the disease process to be useful for current and future therapeutic approaches that centre on disease modification. As a result, in recent years increasing research attention has been given to mild cognitive impairment (MCI) and the diagnosis of prodromal dementia. Petersen et al. (1999) described MCI as an entity with clinical characteristics intermediate between dementia and healthy controls, and high rates of conversion to dementia [most commonly Alzheimer’s disease (AD) because of the amnestic weighting of the MCI definition]. Later, the diagnosis was refined to subcategorize MCI into amnestic (aMCI) and non-amnestic MCI (naMCI), depending on whether memory was affected or not (Petersen et al. 2001; Winblad et al. 2004). aMCI was hypothesized to precede AD or vascular dementia whereas naMCI was thought to be more likely to precede dementia with Lewy bodies (DLB), vascular dementia or frontotemporal dementia (Petersen, 2004).

More recently, criteria for the diagnosis of MCI due to AD (Albert et al. 2011) and prodromal AD (Dubois et al. 2010) have been put forward. These diagnostic criteria are similar to previous descriptions of aMCI but also include validated disease biomarkers indicative of brain amyloid deposition and/or neuronal injury.

The diagnosis of prodromal dementia has gained prominence following disappointing results in recent trials of anti-amyloid therapies and the hypothesis that such treatments may only be successful in the earliest stages of the disease (Aisen et al. 2013). AD, the most common type of dementia, has received significant attention in this regard. A wide variety of other causes of dementia exist, with vascular dementia, DLB and frontotemporal dementia being among the most common subtypes. Less common subtypes account for a significant proportion of dementia cases, particularly in those under 65 years old (Harvey et al. 2003). Huntington’s disease has demonstrated a long prodromal phase that has been characterized in recent
longitudinal studies (Paulsen et al. 2008; Tabrizi et al. 2012).

DLB is the second most common type of neurodegenerative dementia after AD, accounting for at least 4.2% of all diagnosed dementias in the community and 7.5% of those in secondary care (Vann Jones & O’Brien, 2014). There are validated consensus criteria for the clinical diagnosis of DLB (McKeith et al. 2005). These display high positive predictive values for the post-mortem neuropathological classification of intermediate- or high-likelihood DLB (Fujishiro et al. 2008). DLB requires different management from AD, most notably the avoidance of antipsychotic medications (Ballard et al. 1998).

The existence of a prodromal phase of DLB is to be expected, given the insidiously progressive nature of the disorder, as with AD. It may also be expected that prodromal DBL should display some of the features characteristic of established DLB (Table 1) (McKeith et al. 2005; Troster, 2008). The identification of a DLB prodrome would enable investigation of the early pathophysiology of DLB and the development of treatments to interrupt these pathophysiological processes. Prodromal DLB may require different management from other dementia syndromes. For example, DLB may potentially be more responsive to cholinesterase inhibition in its prodromal phase, given the early and widespread cholinergic losses seen in DLB compared with AD (Tiraboschi et al. 2002).

In this paper we review the evidence to determine if DLB has a characteristic prodromal phase that may allow its differentiation from other dementia prodromes.

Method

A Medline (Web of Knowledge; 1950 to present) search was carried out in October 2013. The search algorithm used was: ['MCI' OR 'mild cognitive impairment' OR 'mild dementia' OR 'prodromal'] AND ['Lewy'].

The search identified 378 English-language papers. Titles and abstracts were then screened by two reviewers (P.C.D. and A.J.T.). Case studies were excluded. In longitudinal cohorts where the same outcomes had been reported at different time points, only the most recent results were included. A total of 54 relevant papers were identified. After reading these papers, it was apparent that the original search did not find a significant number of relevant papers investigating rapid eye movement (REM) sleep behaviour disorder (RBD) as a prodrome of DLB.

A second search was carried out using the terms ['RBD' OR 'REM sleep behaviour disorder' OR 'rapid eye movement sleep behaviour disorder'] AND ['Lewy']. Of 108 further results, 15 papers of interest were identified.

After further assessment, 29 papers were found to contain original data on prodromal DLB. A further paper was found after searching the bibliographies of these papers (Postuma et al. 2011).

Results

Epidemiological studies of rates of conversion from MCI to DLB

Three studies have prospectively followed up patients with MCI for the development of DLB. In a cohort of 581 75-year-olds (440 cognitively healthy, 48 with aMCI and 93 with nMCI) followed up for 30 months, possible DLB was found in 10 cases, all of whom also fulfilled clinical criteria for possible or probable AD (Fischer et al. 2007). At baseline, four were cognitively healthy, two had aMCI and four had nMCI. In another group of 133 patients with MCI followed up for 6 years, 53.4% developed dementia and 5.6% (4/71) of these dementia cases were diagnosed as DLB (Palmqvist et al. 2012). One study that followed up 170 consecutive cases of MCI at a memory clinic found high rates of DLB (22% of dementia cases were probable DLB, 6% were possible DLB) (Bombois et al. 2008). The heterogeneity of these results can be attributed, at least partly, to the recruitment of participants, with the highest proportions of DLB found in a study

Table 1. Diagnostic features of DLB (adapted from McKeith et al. 2005)

| Pattern of cognitive deficits: impairments of attention, executive and visuospatial function |
| Core features: spontaneous parkinsonism, complex visual hallucinations, fluctuating cognition |
| Suggestive features: REM sleep behaviour disorder (RBD), neuroleptic sensitivity, reduced dopamine transporter density in the striatum |
| Supportive features: repeated falls/syncope, transient unexplained loss of consciousness, autonomic dysfunction, depression, hallucinations, delusions |
| Imaging findings and other biomarkers: preservation of medial temporal lobe structures on structural imaging, reduced occipital perfusion, abnormal MIBG myocardial scintigraphy, EEG abnormalities |

REM, Rapid eye movement; MIBG, metaiodobenzylguanidine; EEG, electroencephalography.
recruiting from a tertiary referral centre (Bombois et al. 2008) and the lowest in a study that recruited most patients from primary care units (Palmqvist et al. 2012).

In a post-mortem study of 134 patients who died with a diagnosis of MCI, eight (6%) had cortical Lewy bodies (LBs); five of these eight in the absence of vascular or AD pathology. A further 10% had nigral or limbic LBs (Schneider et al. 2009). Saito & Murayama (2007) found that, of 33 MCI cases showing degenerative pathology post-mortem, six (18%) had LB pathology, with half of these showing only DLB-type changes. Another small study of an aMCI group found that one in 15 cases had transitional LB pathology post-mortem, along with some AD pathology (Petersen et al. 2006).

Table 2. The prevalence of key symptoms in three clinical studies of prodromal DLB

| Symptom Category            | Auning et al. 2011 (%) | Chiba et al. 2012 (%) | Fujishiro et al. 2013 (%) |
|-----------------------------|------------------------|-----------------------|---------------------------|
| Cognitive problems          |                        |                       |                           |
| Memory                      | 57                     | 100                   | 100                       |
| Problem-solving             | 33                     |                       |                           |
| Language                    | 16                     |                       |                           |
| Fluctuations                |                        |                       |                           |
| Neuropsychiatric symptoms   |                        |                       |                           |
| Visual hallucinations       | 44\*                   | 31                    |                           |
| Depression                  | 34                     | 24                    | 19                        |
| Anxiety                     | 26\*                   |                       |                           |
| Lack of motivation          |                        |                       | 26                        |
| Locomotor symptoms          |                        |                       |                           |
| Tremor/stiffness            | 25\*                   | 27\*                  | 31                        |
| Gait problems               | 27\*                   |                       |                           |
| Falls                       | 13\*                   |                       |                           |
| Extrapyramidal signs        |                        |                       | 31                        |
| Autonomic symptoms          |                        |                       |                           |
| Constipation                | 47\*                   | 57                    |                           |
| Orthostatic dizziness       | 24\*                   | 18                    |                           |
| Urinary incontinence        | 27                     | 8                     |                           |
| Increased salivation        | 21\*                   |                       |                           |
| Sleep symptoms              |                        |                       |                           |
| Sleep rhythm change         | 62\*                   | 62\*                  |                           |
| Crying/shouting in sleep    | 62\*                   |                       |                           |
| Limb movements              | 35\*                   |                       |                           |
| Nightmares                  | 27\*                   |                       |                           |
| RBD                         |                        |                       | 46                        |
| Other                       |                        |                       |                           |
| Anosmia/hyposmia            | 41\*                   | 38                    |                           |

DLB, Dementia with Lewy bodies; RBD, rapid eye movement (REM) sleep behaviour disorder.
\* Significantly more common than Alzheimer’s disease (AD) comparison group (no comparison group in Fujishiro et al. 2013).

Clinical studies of prodromal DLB

Three studies (Auning et al. 2011; Chiba et al. 2012; Fujishiro et al. 2013) have asked patients with DLB and/or their carers to retrospectively report on the early symptoms of DLB (Table 2).

Auning et al. (2011) interviewed carers of patients newly diagnosed with mild DLB about the presenting symptoms of DLB (MMSE>20; n=61). Visual hallucinations (44%), gait problems (28%), tremor/stiffness (25%) and a tendency to fall (13%) were significantly more common in DLB compared with an AD control group whereas memory problems were significantly less common. Fluctuating cognition was not offered as an option for a presenting symptom. Carers did have the opportunity to report symptoms not on the
preselected list but any other reported symptoms were infrequent (<10%).

Chiba et al. (2012) asked patients and carers to fill in a survey of predefined symptoms without any additional instructions. They looked at the temporal onset of symptoms relative to memory loss. This was to allow comparison of DLB (n=34) and AD (n=32), both of which are associated with progressive memory impairment. The most common symptoms present in the same year as the onset of memory loss were sleep rhythm change (62%), crying/shouting in sleep (62%), anosmia/hyposmia (41%), constipation (47%) and limb movements in sleep (35%) (Table 2). Of those symptoms that were more common in DLB than AD, the earliest to develop were constipation (mean=9.4 years before memory impairment), crying/shouting during sleep (4.9 years), limb movements during sleep (3.9 years), anosmia/hyposmia (2.9 years) and nightmares (2.5 years). The three symptoms taken to be most representative of DLB (due to high prevalence in DLB and relatively low prevalence in AD/controls) were crying/shouting during sleep, constipation and anosmia/hyposmia. One or more of these symptoms differentiated DLB from AD with a sensitivity of 0.71 and a specificity of 0.81. Increasing the threshold to two or more symptoms resulted in a decrease in sensitivity to 0.38 but an increase in specificity to 0.97. The questionnaire did not enquire about parkinsonism, hallucinations or fluctuations.

The same group later assessed the presence and time of onset of core features and eight symptoms of LB disease in 90 patients with probable DLB (Fujishiro et al. 2013). There was no comparison group. As with the previous study, the presence of each symptom at the onset of memory loss was recorded. This study found rates of constipation, anosmia/hyposmia, RBD, depression and orthostatic dizziness comparable to their previous study (Table 2). Lower rates of urinary incontinence were found (8%), and syncope was relatively rare (7%).

This study confirmed that constipation, anosmia and RBD often precede the onset of memory loss by several years. Visual hallucinations and extrapyramidal symptoms each were present in around one-third of individuals at the onset of memory loss, although on average these symptoms developed 1.5 years after memory loss.

Post-mortem studies of prodromal symptoms of DLB
Some post-mortem studies of established DLB have retrospectively assessed the chronological development of symptoms. Ferman et al. (2011) examined 98 patients with intermediate-high likelihood of DLB on post-mortem examination who had been part of a longitudinal study. On average, RBD preceded dementia by 6 years [with wide variation (s.d.=12 years), possibly reflecting some cases with very early onset RBD]. Conversely, visual hallucinations and parkinsonism followed the estimated dementia onset by an average of 2.6 and 1.8 years respectively. Another Mayo Clinic post-mortem study examined 52 patients diagnosed during life with probable or possible DLB (Fujishiro et al. 2008). The authors remarked that ‘RBD antedated the diagnosis of DLB in almost all cases in which RBD was noted’, whereas the presence of notable visual hallucinations followed the development of dementia by an average of 2.8 years.

Both of the above studies recruited subjects when they had already been diagnosed with dementia and prospectively collected information through regular clinical and neuropsychiatric assessments. Two further studies specifically recruited non-demented subjects for prospective follow-up. These studies reported a different pattern of symptom development in prodromal DLB.

Jicha et al. (2010) enrolled cognitively normal patients for regular clinical follow-up and brain donation following death. Nine patients with neocortical DLB post-mortem and no significant AD or vascular pathology had an identified MCI phase during their illness. This group was compared with 12 patients with a post-mortem diagnosis of AD. None of the AD-MCI group displayed parkinsonism, cognitive fluctuations or psychiatric symptoms (hallucinations/delusions/paranoia) during the MCI phase. Eight of nine MCI-DLB demonstrated at least one of these features concurrent with the MCI diagnosis (parkinsonism n=5; fluctuations n=3; psychiatric symptoms n=4). MCI-DLB was associated with significant memory impairment but the group performed better on immediate recall than AD-MCI. They were worse on phonemic fluency and tended towards being worse at trail-making, but were better at the Boston Naming Test. It should be noted that, because of the strict inclusion criteria, these findings only represent the MCI phase of patients with later neocortical LB deposition (i.e. a subset of all those who have DLB, some of whom will not have cortical involvement) and without significant vascular or AD pathology.

In a similar study, Molano et al. (2010) identified eight patients from their research databases who had been prospectively followed up after a diagnosis of MCI, and later were found to have LB disease post-mortem (limbic or neocortical predominant). In the year of MCI diagnosis, or preceding this, five displayed parkinsonism and three had visual hallucinations whereas none displayed fluctuations. RBD was present in seven cases at the diagnosis of MCI, preceding it by up to 47 years. Seven cases developed
dementia before death. Of these, five had parkinsonism, five had hallucinations and two had fluctuations before the development of dementia. The patients had a variety of MCI subtypes. Attention/executive function ($n=6$) and visuospatial function ($n=6$) were the cognitive domains most commonly affected.

**Imaging findings in prodromal DLB**

Six studies have performed imaging in MCI subjects who later developed DLB. In the study by Molano et al. (2010), three cases had serial magnetic resonance imaging (MRI). Compared with previously published data, hippocampal volumes at the time of MCI and the rate of hippocampal atrophy were within the range of cognitively normal subjects.

In a group of 170 patients with MCI, baseline subcortical hyperintensities on MRI were associated with an increased risk of developing mixed or vascular dementia, but not DLB or other dementia subtypes (Bombois et al. 2008).

One study has performed positron emission tomography (PET) dopamine terminal imaging on subjects with MCI with follow-up for the development of DLB (Albin et al. 2013). Of 27 MCI subjects, two had markedly reduced striatal $^{11}$C-dihydrotetabenazine (DTBZ) binding. Both developed dementia at follow-up; one was classified as DLB, the other as frontotemporal dementia. However, three out of 25 MCI subjects with normal DTBZ scans also developed DLB.

Clerici et al. (2009) performed $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) PET on 16 patients with single domain aMCI and 14 patients with naMCI with executive dysfunction. These were compared with controls who were undergoing PET scans for cancer restaging. Of those who completed follow-up, one in 14 aMCI and five in 12 naMCI developed DLB. In a voxel-based analysis, the naMCI who developed DLB had heterogeneous patterns of hypometabolism compared to controls. The inferior and mesial frontal areas, anterior and posterior cingulate areas, and superior temporal and inferior parietal areas were most frequently involved. Frontal hypometabolism may have been expected, given that executive dysfunction was one of the inclusion criteria for the naMCI group. This may not be representative of all prodromal DLB.

Fardo et al. (2010) followed 19 army veterans with MCI for 3 years following baseline FDG-PET scans. Two developed DLB; both had an ‘AD-like’ pattern of hypometabolism (hypometabolism in medial parietal and lateral parietal regions) on visual inspection. Neither displayed occipital hypometabolism.

Another study performed MR spectroscopy, diffusion weighted imaging (DWI) and perfusion imaging on 119 patients with MCI (Fayed et al. 2008). After follow-up, subjects could be classified as AD (including mixed dementia, $n=49$), Lewy body dementia (LBD) ($n=5$; criteria not stated), MCI due to vascular disease ($n=15$), MCI due to depression ($n=22$) or MCI due to AD ($n=28$). There were no differences between LBD and the other groups in baseline spectroscopy or perfusion findings. On DWI in the right hippocampus, the LBD group had higher baseline apparent diffusion coefficient (ADC) values compared with the three MCI groups, indicating greater white matter disruption. The difference between LBD and AD approached significance ($p=0.08$). Values in the AD/mixed dementia group did not differ from the MCI groups. Baseline characteristics were not provided, so the findings could be due to differences between groups at baseline (e.g. age or severity of cognitive impairment).

**RBD**

RBD is associated with high rates of conversion to dementia. Longitudinal studies have estimated that over half of patients with RBD go on to develop a neurodegenerative disorder that is nearly always a synucleinopathy [e.g. Parkinson’s disease (PD), PD dementia, DLB, multi-system atrophy] if followed up for more than a decade, rising to up to 93% if followed up over longer periods (Postuma et al. 2009; Iranzo et al. 2013; Schenck et al. 2013). In these studies, 14–39% of those who developed a neurodegenerative disorder were diagnosed with DLB.

Studies specifically looking at DLB with RBD have confirmed that RBD tends to precede cognitive symptoms by several years (Boeve et al. 1998, 2003). In some cases the gap is more than 25 years (Claassen et al. 2010). Core symptoms may develop earlier in DLB patients with RBD than in those without RBD (Dugger et al. 2012).

**Imaging in RBD to predict the development of DLB**

Dang-Vu et al. (2012) performed technetium-99m ethylcysteinate dimer ($^{99m}$Tc-ECD) single photon emission computed tomography (SPECT) perfusion scanning on 20 patients with RBD who did not have dementia (although 13 had MCI), and compared these to 10 healthy controls. After an average follow-up of 3 years, five RBD subjects developed DLB (criteria not stated) and five PD. All those who developed DLB had an initial diagnosis of MCI. The PD/DLB group had increased baseline hippocampal regional cerebral blood flow (rCBF) compared to the RBD group that did not develop neurodegenerative disease. The five DLB patients had increased hippocampal rCBF compared with controls. There were no significant differences between the PD and DLB groups.
The PD/DLB group was on average 4.8 years older than the RBD subjects who did not develop disease. Iranzo et al. (2010) performed striatal dopamine terminal binding of \( ^{123}I-2\beta\)-carbomethoxy-3\(\beta\)-(4-iodophenyl)-N-(3-fluoropropyl)nortropane (\( ^{123}I\)-FP-CIT) and transcranial echosonography of the substantia nigra in 43 patients with RBD. Eight patients later developed neurodegenerative disease (five PD, two DLB and one multi-system atrophy), all of whom had at least one abnormal imaging finding. Thirty percent of those with an abnormal finding developed a neurodegenerative disease at 2.5 years, compared with none of those with two normal scans. Both DLB cases displayed substantia nigra hyperechogenicity and one had reduced striatal \( ^{123}I\)-FP-CIT uptake at baseline.

Other biomarkers in RBD to predict the development of DLB

Postuma and colleagues commenced a longitudinal study of RBD in 2004. After several years they have been able to identify baseline symptoms and signs that were associated with the development of neurodegenerative disease. In their latest report (Postuma et al. 2013), 32 of 91 RBD subjects in their cohort had developed neurodegenerative disease (11 probable DLB, four possible DLB, 17 parkinsonism). This group reported greater baseline levels of urinary dysfunction, erectile dysfunction and constipation than controls. They did not report more symptoms of orthostatic hypotension but did have a greater postural drop in blood pressure. These abnormalities were present \( \geq 4 \) years before the development of neurodegenerative disease. The results for the RBD group without neurodegenerative disease were intermediate between the controls and the disease group, possibly reflecting that some of this group were in the process of developing a neurodegenerative disease. Baseline postural hypotension and urinary dysfunction were significantly more common in the disease than in the non-disease RBD group. Electrocardiography (ECG) measures of autonomic dysfunction (including constipation and orthostatic dizziness), hyposmia, visual hallucinations and motor symptoms. Even without including core symptoms, prodromal DLB may be distinguished from prodromal AD with reasonable sensitivity and specificity (Chiba et al. 2012). The earliest symptoms of DLB are constipation, RBD and hyposmia. RBD has been demonstrated to precede DLB by decades in some cases. Table 3 shows approximate temporal relationships between symptoms in prodromal DLB from the evidence currently available. The order of symptom development is similar to that reported in PD (Gaenslen et al. 2011).

Motor abnormalities assessed by the Unified Parkinson’s Disease Rating Scale (UPDRS), the alternate-tap test, the Purdue Pegboard and the timed up-and-go were all found to be abnormal in DLB at least 3 years before the diagnosis of dementia (Postuma et al. 2012). These tests seemed to be abnormal for longer periods before the development of DLB than PD.

Patients who developed DLB or PD dementia had abnormal baseline colour vision and olfactory function, assessed using the Farnsworth-Munsell-100-Hue and University of Pennsylvania Smell Identification tests respectively (Postuma et al. 2011). These abnormalities were present at the first assessment, up to 5 years before the development of dementia. Those with both abnormal olfaction and colour vision had an estimated disease-free survival (i.e. no DLB, PD dementia or PD) of 18%, compared with 82% of those with normal function on both tests.

In general, each of the abnormalities discussed above had high specificity but low sensitivity in identifying those with RBD who would go on to develop neurodegenerative disease. The abnormalities were present some years before the diagnosis of disease and tended to progress slowly.

Discussion

Clinical presentation of prodromal DLB

The evidence suggests that DLB can be preceded by an MCI phase before the development of dementia. Two studies that followed up participants with MCI for the development of DLB (Fischer et al. 2007; Palmqvist et al. 2012), reported figures similar to reported rates of DLB in clinically diagnosed dementia samples (Vann Jones & O’Brien, 2014), although the rates varied greatly between studies, probably because of recruitment from different clinical populations. Although the data available are limited, the pattern of symptoms in prodromal DLB seems to differ from that of prodromal AD. Particular symptoms that are more frequent in prodromal DLB include RBD, autonomic dysfunction (including constipation and orthostatic dizziness), hyposmia, visual hallucinations and motor symptoms. Even without including core symptoms, prodromal DLB may be distinguished from prodromal AD with reasonable sensitivity and specificity (Chiba et al. 2012). The earliest symptoms of DLB are constipation, RBD and hyposmia. RBD has been demonstrated to precede DLB by decades in some cases. Table 3 shows approximate temporal relationships between symptoms in prodromal DLB from the evidence currently available. The order of symptom development is similar to that reported in PD (Gaenslen et al. 2011).

Prodromal DLB can present with either amnestic or non-amnestic cognitive impairment (Fischer et al. 2007; Clerici et al. 2009; Molano et al. 2010), although visuospatial and executive function may be particularly likely to be affected (Molano et al. 2010). This is supported by findings in a recent study comparing neuropsychological measures at initial presentation (including MCI and mild dementia cases) (Yoshizawa et al. 2013). Those with ‘pure’ DLB pathology at post-mortem had greater visuospatial impairment and less memory impairment at initial assessment compared to ‘pure’ AD or mixed DLB+AD pathology groups.
There is conflicting evidence on when the core features of DLB develop. Two longitudinal post-mortem cohorts that recruited subjects with dementia found that core features developed after the onset of dementia (Fujishiro et al. 2008; Ferman et al. 2011). Conversely, two longitudinal post-mortem studies that recruited subjects before the onset of dementia (Jicha et al. 2010; Molano et al. 2010) and two retrospective interview studies (Auning et al. 2011; Fujishiro et al. 2013) found that core symptoms commonly develop before the onset of dementia. These studies differed greatly in design and selection criteria, which may account for the differences in findings. The duration of dementia before death was notably different between some of the studies (4 years in Molano et al. (2010) versus 8–10 years on average in the two cohorts that recruited dementia patients (Fujishiro et al. 2008; Ferman et al. 2011)]. This suggests that the studies may have recruited cohorts that were not clinically similar, or that diagnostic thresholds were different between the studies.

From this evidence, it seems that most cases of prodromal DLB will display clinical and neuropsychological characteristics similar to established DLB. There has been little investigation into the use of imaging and other biomarkers to identify prodromal DLB. Indeed, we did not find any studies that investigated cerebrospinal fluid (CSF) biomarkers in prodromal DLB. Autonomic symptoms are common in prodromal DLB (Chiba et al. 2012); objective biomarkers of autonomic function such as postural hypotension could potentially be useful in the diagnosis of prodromal DLB.

Biomarkers of prodromal DLB

There has been little investigation into the use of imaging and other biomarkers to identify prodromal DLB. Indeed, we did not find any studies that investigated cerebrospinal fluid (CSF) biomarkers in prodromal DLB. Autonomic symptoms are common in prodromal DLB (Chiba et al. 2012); objective biomarkers of autonomic function such as postural hypotension could potentially be useful in the diagnosis of prodromal DLB.

Dopamine terminal imaging can be abnormal in mild DLB in the absence clinical features of parkinsonism, suggesting that it may have a role in identifying prodromal DLB (Auning et al. 2011; Siepel et al. 2013). The only paper to investigate this (Albin et al. 2013) found that one of two MCI subjects with baseline striatal dopaminergic denervation later developed DLB. Three other subjects who developed DLB had normal dopamine terminal scans in the MCI phase. The same authors had previously reported a case of rapid striatal dopaminergic denervation around the time of onset of DLB (Albin & Koeppe, 2006).

With regard to other imaging modalities, raised hippocampal diffusivity on DWI compared with controls was found in one study, but this was not significantly greater than in the prodromal AD group (Fayed et al. 2008). Surprisingly, the typical DLB pattern of occipital hypometabolism was not found in the few patients who had FDG-PET scans in the prodromal stage of the illness (Clerici et al. 2009; Pardo et al. 2010).

In summary, it seems that striatal dopaminergic innervation is abnormal in some, but not all, patients with prodromal DLB; occipital hypometabolism may be a less sensitive marker of DLB in the prodromal phase. Further research is needed to evaluate the usefulness of these imaging modalities and others.
known to be abnormal in established DLB, such as cardiac iodine-123-metaiodobenzylguanidine (\textsuperscript{123}I-MIBG) scintigraphy.

**RBD as a prodrome of DLB**

RBD patients represent a particular cohort at risk for developing DLB. Poor olfaction and colour vision, autonomic and motor dysfunction, reduced striatal dopaminergic innervation on SPECT, substantia nigra hyperperfusion and substantia nigra hyperechogenicity may all help to predict those with RBD who will go on to develop DLB or PD (Iranzo et al. 2010; Postuma et al. 2010, 2011, 2012, 2013; Dang-Vu et al. 2012). None of these markers differentiate between those who will develop DLB and those who will develop PD. The evidence for these biomarkers is generally based on small DLB samples and none of the findings have been replicated. Findings in RBD groups may not be generalizable to the wider prodromal DLB population.

**Limitations**

With the exception of three retrospective symptom questionnaire studies (Auning et al. 2011; Chiba et al. 2012; Fujishiro et al. 2013), most of the evidence relates to small groups of DLB patients. Few findings have been replicated.

In general, the evidence is from clinical studies, without post-mortem verification of diagnosis. In some cases, this may have led to false positive or false negative results because of the misclassification of study subjects, and such misclassification would in turn affect the performance of biomarkers. Because of the heterogeneity of the data available, it is not possible at this stage to combine the data or objectively compare the reliability of conflicting findings. This prevents us from objectively testing whether DLB has a distinct prodrome using these data. Longitudinal studies are required, first to develop criteria for the prodrome of DLB and then to test their validity.

**Conclusions**

The evidence available, although limited, suggests that DLB has an identifiable prodromal phase in most cases. It may be possible to differentiate prodromal DLB from prodromal AD based on the presence of core and suggestive features of DLB, autonomic dysfunction and other biomarkers. \textsuperscript{123}I-FP-CIT and \textsuperscript{123}I-MIBG SPECT findings are abnormal in established DLB. It remains to be ascertained at what point in the evolution of the disease these findings become abnormal, and if these scans will be clinically useful in the identification of prodromal DLB.

Longitudinal studies are certainly needed to further characterize the clinical presentation of prodromal DLB and investigate the utility of biomarkers (including CSF biomarkers) in its identification. Interesting findings in RBD suggesting that olfactory, visual, autonomic and motor dysfunction, and hippocampal hyperperfusion and substantia nigra hyperechogenicity, may predict the development of DLB should be investigated in a ‘normal’ MCI group, not recruited in a specialist sleep disorders centre.

Characterization of the DLB prodrome is vital to enable the identification of DLB patients in the prodromal stage. This will facilitate research into the pathophysiology of prodromal DLB and the development of treatments aimed at halting or reversing these pathophysiological processes.

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**Declaration of Interest**

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