Donaghy PC, Barnett N, Olsen K, Taylor J-P, McKeith IG, O'Brien JT, Thomas AJ.

Symptoms associated with Lewy body disease in mild cognitive impairment.

***International Journal of Geriatric Psychiatry* (2017)**

DOI: https://doi.org/10.1002/gps.4742

Title Page

Title

Symptoms Associated with Lewy Body Disease in Mild Cognitive Impairment.

Running Head

Symptoms associated with Lewy body MCI

Keywords

Lewy

Dementia

Mild cognitive Impairment

Prodromal

Symptom

Key points

Many symptoms of Lewy body disease can be present even at the MCI stage

REM sleep behaviour disorder and hyposmia may be the earliest symptoms of Lewy body disease

Autonomic symptoms and hyposmia are not specific to Lewy body disease

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Sponsor

This research was supported by the NIHR Newcastle Biomedical Research Unit

Grant Numbers: BH120812, BH120878

Conflicts of Interest

None

Word Count of body text

3463

Abstract

Objective

Dementia with Lewy bodies (DLB) is associated with a range of cognitive and non-cognitive symptoms. We aimed to identify if some of these symptoms might aid early diagnosis of Lewy body disease in cases of mild cognitive impairment (MCI).

Methods

Lewy body MCI (MCI-LB; n=36), Alzheimer's disease MCI (MCI-AD; n=21), DLB (n=36), AD (n=21) and control (n=20) participants were recruited. An interview-based questionnaire about the presence of symptoms thought to be associated with Lewy body disease was completed by participants with, where possible, their carer/relative. The prevalence of each symptom was compared between MCI-LB and MCI-AD and between established DLB and AD and a symptom scale based on these findings was devised.

Results

Fluctuating concentration/attention; episodes of confusion; muscle rigidity; changes in hand-writing, gait and posture; falls; drooling; weak voice; symptoms of REM sleep behaviour disorder (RBD) and misjudging objects were more common in MCI-LB compared with MCI-AD, and also in DLB compared with AD. Hyposmia, tremor, slowness and autonomic symptoms were not specific to Lewy body disease. RBD and hyposmia were reported to develop several years prior to the onset of cognitive symptoms in Lewy body

disease. A ten-point symptom scale differentiated between MCI-LB and MCI-AD with a sensitivity of 83% and a specificity of 100%.

Conclusions

Drooling, misjudging objects and symptoms related to parkinsonism, fluctuating cognition and RBD may be the most characteristic symptoms of MCI-LB. Slowness, tremor, autonomic symptoms and hyposmia are all common in MCI-LB but are not specific to the disease.

Word count: 249

Introduction

Dementia with Lewy bodies (DLB) is the second most common type of neurodegenerative dementia after Alzheimer's disease (AD), accounting for 7.5% of cases in secondary care (Vann Jones and O'Brien 2014). In 2005, International Consensus Criteria identified spontaneous motor parkinsonism, recurrent visual hallucinations, cognitive fluctuations, REM sleep behaviour disorder (RBD) and neuroleptic sensitivity as symptoms diagnostic of DLB, with an additional biomarker of reduced striatal dopaminergic innervation on PET or SPECT imaging (McKeith, et al. 2005). A range of other symptoms including repeated falls and syncope, unexplained loss of consciousness, hallucinations in non-visual modalities, delusions, depression and autonomic dysfunction were identified as being commonly present but of unknown diagnostic specificity.

The varied nature of symptoms associated with DLB is likely to reflect the widespread deposition of Lewy body pathology in both the peripheral and central nervous systems. Sites such as the olfactory bulb and autonomic nervous system may be early sites of pathology in many cases (Beach, et al. 2009; Beach, et al. 2010). This raises the possibility of identifying LB disease in its early stages, prior to the development of dementia, through non-cognitive symptoms such as hyposmia, constipation and postural hypotension.

Prospective clinical studies and post-mortem studies have reported that the diagnostic symptoms of DLB may already be present in the MCI phase of the disease (Cagnin, et al. 2015; Ferman, et al. 2011; Ferman, et al. 2013; Fujishiro, et al. 2008; Yoon, et al. 2015). In particular RBD appears to be the most common and earliest-developing diagnostic symptom in this phase (Ferman et al. 2011). Retrospective studies based on symptom questionnaires have replicated these findings, with visual hallucinations, gait problems, tremor/stiffness,

falls and sleep symptoms including RBD reported as more common in early stages of disease in DLB than AD, in addition to other symptoms such as hyposmia and constipation (Auning, et al. 2011; Chiba, et al. 2012; Donaghy, et al. 2015).

This study investigated the prevalence of a broad range of symptoms associated with Lewy body disease in the mild cognitive impairment phase (MCI-LB) compared with MCI-AD. The same symptoms were also examined in patients with established DLB and AD to compare the findings. The aim was to identify symptoms that might be useful to clinicians and researchers to help identify MCI-LB and distinguish it from MCI-AD.

Methods

Participants

DLB, AD, MCI-LB, MCI-AD and control subjects were recruited prospectively from secondary care services in the North of England. Control participants were recruited through a research case register or were partners of participants.

Dementia participants were ≥60 years old and had a diagnosis of probable dementia with Lewy bodies or probable Alzheimer's disease confirmed by two clinicians based on current diagnostic criteria (McKeith et al., 2005, McKhann et al., 2011), with an MMSE score ≥12. MCI participants were recruited for a study investigating prodromal DLB in which all participants had to have a possible symptom of Lewy body disease to be recruited to the study (e.g. tremor, unusual visual experiences, daytime sleepiness, sleep disturbance). All participants fulfilled criteria for all-cause MCI (Albert, et al. 2011), had an MMSE >20 and Clinical Dementia Rating score of ≤0.5.

The diagnosis of MCI and the presence or absence of diagnostic symptoms of Lewy body disease as defined by consensus criteria (McKeith et al. 2005) was determined by a three clinician panel (PD, AT, JPT). Following the clinical and cognitive examination two clinicians rated whether the core and suggestive diagnostic symptoms of DLB were present in each participant. If there was disagreement between these two raters, the third clinician made the final decision. MCI subjects had ^{123}I-FP-CIT SPECT but classification of the presence or absence of diagnostic symptoms was carried out blind to FP-CIT imaging results. Participants that were found to have no core or suggestive diagnostic features of Lewy body disease and had a negative ^{123}I-FP-CIT SPECT fulfilled the clinical criteria for MCI-AD (Albert et al. 2011). MCI participants with two or more International Consensus Criteria Core or Suggestive Features (McKeith et al. 2005) were classified as Lewy body MCI (MCI-LB). When parkinsonian symptoms were present, participants were only included if the onset of these was after, or less than one year prior to the onset of cognitive symptoms. Participants with only one core or suggestive feature were excluded from further analysis.

Control participants had an MMSE ≥26 and no evidence of MCI or dementia. Participants were excluded if they had a major concurrent psychiatric illness; severe physical illness that would limit their ability to fully participate in the study; a history of other significant neurological illness including clinical stroke or current treatment with any investigational agent.

All participants with capacity gave their written informed consent to take part in the study. In the case of participants with dementia who lacked capacity their participation in the study was discussed with a consultee in accordance with the Mental Capacity Act. The study

received ethical approval from the National Research Ethics Service Committee North East - Newcastle & North Tyneside 2 (Research Ethics Committee Identification Numbers: 13/NE/0064, 12/NE/0290).

Clinical Assessment

All patients were assessed by the equivalent of a Board Certified Psychiatrist, who carried out a physical and neurological examination. Quantitative scales were used to assess neuropsychiatric symptoms (Geriatric Depression Scale (D'Ath, et al. 1994), Clinician Assessment of Fluctuations (Walker, et al. 2000), Dementia Cognitive Fluctuations Scale (DCFS) (Lee, et al. 2014), Neuropsychiatric Inventory (Cummings, et al. 1994)), parkinsonism (Revised Unified Parkinson's disease Rating Scale Motor Sub-scale (Goetz, et al. 2008)) and level of functional impairment (Instrumental Activities of Daily Living Scale (Lawton and Brody 1969)). These assessments were used by the diagnostic panels detailed above to help determine each participant's diagnosis.

The Lewy Body Symptom Questionnaire

Participants (with a relative or carer when possible) were interviewed and asked whether they experienced each of the symptoms listed in Table 1. The symptom list was adapted from an early version of the Lewy Body Dementia Association (LBDA) Comprehensive Symptom Checklist (an updated version of which is available at: www.lbda.org/content/comprehensive-lbd-symptoms-checklist). The checklist was

developed by the LBDA to help people with Lewy body dementia and their carers identify symptoms that can then be reported to their physician during appointments.

The interviewer asked if each individual symptom was present. Efforts were made to ensure the participants understood the question (e.g. ensuring that they understood that rigidity referred to muscles and not joints). In accordance with the purpose of the checklist, where participants understood the question their response was accepted without interpretation by the interviewer (e.g. including affirmative responses to 'seeing things that are not present' even if this seemed to refer to a misidentification rather than a hallucination). Where a symptom was present, participants were asked to estimate how long the symptom has been present for.

Some questions were changed or added after commencing the studies, reflecting changes to the LBDA Checklist (e.g. weak voice, balance problems, frequent falls, anxiety, reaction to medications) and new evidence on visual symptoms in DLB (Jefferis, et al. 2013). As a result, the number of respondents differed between questions. The minimum number of respondents for each symptom was 29 for MCI-LB, 19 for MCI-AD, 20 for AD, 32 for DLB and 14 for controls. Sexual dysfunction was part of the original symptom checklist but in a large proportion of cases it was not felt appropriate to enquire about this during the interview (e.g. a widow/widower of several years attending with their son/daughter). Due to insufficient data this symptom was not analysed.

TABLE 1 HERE

Statistics

Two comparisons were carried out for each symptom – MCI-LB v. MCI-AD and DLB v. AD. Control figures are included as a reference. Chi-squared and Fischer's Exact tests were used with an unadjusted α=0.05 for each comparison. To reduce the risk of Type 1 errors, symptoms were only considered significant if they were found to be significantly more common in both Lewy body groups (MCI-LB and DLB) compared to their respective Alzheimer's groups (MCI-AD and AD).

Results

Group demographics are displayed in Table 2. The MCI-LB group was more likely to be male than the MCI-AD group, there was no such difference between DLB and AD as these groups were matched for gender. There were no significant differences in age or overall level of cognitive impairment between the comparator groups (i.e. MCI-LB v. MCI-AD, and DLB v. AD). MCI-LB participants were more likely to live with their informant and have daily contact with them than MCI-AD participants.

TABLE 2 HERE

The proportion of participants from each group experiencing each symptom is displayed in Table 3. Symptoms that were significantly more common in both MCI-LB than MCI-AD and in DLB than AD were: fluctuating attention and concentration, unexplained episodes of confusion, rigidity or stiffness in muscles, shuffling walk, change in handwriting, drooling,

frequent falls, change in posture, weak voice, symptoms of REM sleep behaviour disorder and difficulty moving around due to misjudging where objects are. Three further symptoms were significantly more common in DLB than AD and approached statistical significance in the MCI comparison: slowness of movement (p=0.079), loss of smell (p=0.053) and seeing things that are not present (p=0.052).The reported time of onset of these symptoms relative to the onset of memory impairment in the Lewy body groups is reported in Table 4. The earliest symptoms reported for both groups were loss of sense of smell and symptoms of RBD. Participants in the MCI-LB cohort also reported muscle stiffness/rigidity as an early feature, though it should be noted that only 28% of respondents reported this symptom. Other symptoms were reported to develop after the onset of memory problems.

TABLE 3 HERE

TABLE 4 HERE

Apathy and excessive daytime sleepiness were more common in MCI-LB than MCI-AD, but were not more common in DLB than AD due to the higher prevalence of these symptoms in AD than in the MCI-AD group.

Several symptoms were significantly more common in DLB than AD, but not significantly more common in MCI-LB compared with MCI-AD (p>0.10). These were disorganised speech, slack facial expression, balance problems, hearing things not present, other hallucinations, constipation and double vision.

In the dementia groups, the DLB cohort were likely than AD to report significant improvement (42% v 15%) or minimal improvement (29% v 10%) in response to cholinesterase inhibitors/memantine (p=0.01 DLB v AD). 54% of 13 MCI-LB participants reported significant improvement and 15% reported minimal improvement. There were insufficient volunteers treated with cholinesterase inhibitors/memantine in the MCI-AD group to compare responses.

In a post-hoc analysis, symptoms with a prevalence of >50% in DLB and <20% in AD were identified (Table 5). The aim was to identify symptoms that were common in LB disease and specific to this disorder. Ten symptoms were identified. Following this, the number of these symptoms present in each MCI participant was calculated to investigate the ability of these symptoms to differentiate between MCI-LB and MCI-AD.

The mean score in MCI-LB (n=29) was 4.1±1.9, compared with 0.7±0.7 in MCI-AD (n=19). Using a threshold of >1 this 10-point score yielded a sensitivity of 90% and a specificity of 84% to differentiate MCI-LB from MCI-AD (Area under the Receiver Operating Characteristic (AUROC)=0.87; 95% Confidence Interval (CI)=0.75-0.99). A threshold of >2 gave a sensitivity of 83% and a specificity of 100% (AUROC=0.91; 95% CI=0.83-0.999). A threshold of >3 yielded a sensitivity of 62% and a specificity of 100% (AUROC=0.81; 95% CI=0.69-0.93).

TABLE 5 HERE

Discussion

Symptoms reflecting cognitive fluctuations, motor parkinsonism and REM sleep behaviour disorder were more common in LB disease than Alzheimer's disease, both in the early and later stages. These features are used to diagnose DLB and MCI-LB, and therefore by definition will be more common in these groups. However not all symptoms relating to these diagnostic features are specific to the disease. Our data identified which specific symptoms are most useful in distinguishing DLB and MCI-LB from AD and MCI-AD. For instance, rigidity or stiffness in muscles, frequent falls and weak voice were specific symptoms of motor parkinsonism (≤11% in AD and MCI-AD). Conversely, tremor, slowness of movement, change in handwriting and problems with balance were often reported in AD and MCI-AD (≥38%). Interestingly, drooling and misjudging objects were also specific to Lewy body disease despite not being directly related to diagnostic features.

'Seeing things that were not present' was commonly reported in both the MCI-LB and MCI-AD groups. The MCI-AD group were judged by a three-clinician diagnostic panel not to have the typically 'well-formed and detailed' visual hallucinations that constitute a diagnostic feature of DLB. Often the symptoms reported were misidentification phenomena, occurred in low light or were simple hallucinations such as flashes of light. These phenomena are probably less frequent in the general MCI-AD population than in our cohort that was enriched with possible Lewy body symptoms. However, this highlights the importance of assessment by an experienced clinician to properly characterise visual symptoms.

Supportive Features of DLB

Repeated falls and syncope, unexplained loss of consciousness, hallucinations in other modalities, delusions, depression and autonomic dysfunction are included in the 2005 International Consensus Criteria as Supportive Features of Lewy body disease that are commonly present but without proven diagnostic specificity (McKeith et al. 2005). Our data generally supports this decision. Frequent falls were significantly more common in the LB groups but dizziness or fainting was common in all disease groups. Transient loss of consciousness, delusions and depression did not differentiate between Lewy body disease and Alzheimer's disease. Auditory and other hallucinations were more common in DLB than AD, but the overall prevalence was relatively low in both LB groups.

Hyposmia and Autonomic Symptoms

In contrast with a previous retrospective symptom study we did not find that loss of sense of smell, constipation and dizziness differentiated between MCI-LB and MCI-AD (Chiba et al. 2012). Our symptom of 'dizziness or fainting' was different to the 'orthostatic dizziness' reported in that study. Our rates of loss of sense of smell and constipation were similar to Chiba and colleagues, but the rates of these symptoms in MCI-AD and controls were higher in our cohort. The difference in constipation may reflect differences in dietary habits in the UK compared with Japan, or other cultural differences that make the reporting of constipation more likely. Though loss of sense of smell is a common feature of Lewy body disease, it may also be a marker for early Alzheimer's disease (Devanand, et al. 2015) and is therefore unlikely to be a specific marker for either disease.

Duration of symptoms

Only the symptoms of RBD and hyposmia had a reported time of onset before the onset of memory impairment in both MCI-LB and DLB. Other symptoms tended to develop 1-2 years after the onset of memory loss. Previous evidence from longitudinal studies has identified RBD as an early marker or risk factor for the later development of synucleinopathies such as DLB, PDD and multi-system atrophy (Iranzo, et al. 2013).

Symptoms more common in MCI-LB than MCI-AD, but not more common in DLB than AD

Apathy and excessive daytime sleepiness were significantly more common in MCI-LB than MCI-AD. These symptoms may be useful in identifying MCI-LB, but it should be borne in mind that even in MCI-AD apathy (19%) and daytime sleepiness (29%) were not uncommon.

Symptoms more common in DLB than AD, but not more common in MCI-LB than MCI-AD

In addition to constipation, the symptoms of disorganised speech, balance problems, slack facial expression, non-visual hallucinations and double vision were significantly more common in DLB than AD, but the same difference was not observed in the MCI phase. These findings may be due to Type 1 errors or these symptoms may manifest at a later stage of the disease in DLB.

Differentiating MCI-LB from MCI-AD using a 10-point symptom scale

A 10 symptom scale was developed by identifying symptoms that were specific (>80%) and relatively sensitive (>50%) to identify DLB compared with AD. This was then applied to the MCI groups and was found to accurately discriminate between MCI-LB and MCI-AD. There is clearly some circularity here, as six of the ten symptoms directly address diagnostic symptoms (RBD, visual hallucinations and fluctuations) that are used to classify participants as MCI-LB. However, brief assessment scales to identify possible Lewy body disease may be useful to highlight at-risk cases to clinicians, or to aid recruitment to research studies. A previous scale incorporating findings from physical examination for signs of parkinsonism and autonomic features has been shown to reliably identify Lewy body diseases (Galvin 2015). The symptom questionnaire presented here does not incorporate the findings of clinical examination and therefore may be used in different ways. Clearly the questionnaire is not comparable to a clinical history and examination by an experienced clinician. We envisage that such screening questions may be used in initial memory clinic appointments to highlight the need for further assessment or investigation for diagnostic features of DLB and as brief and easily administered questionnaire to identify potential recruits for research studies in DLB and MCI-LB. Sensitivity may be the priority in the former scenario, whereas specificity may be more important in the latter, particularly where larger populations are being screened. The threshold used should be appropriate to the situation.

Strengths and limitations

This is the first cohort to compare the prevalence of a comprehensive range of symptoms between Lewy body disease and Alzheimer's disease in both the MCI and dementia phases. The sample size is large enough to detect large differences, but may not detect small

differences that exist between the two diseases. However, small differences in symptom rates are unlikely to be clinically useful in differentiating MCI-LB from MCI-AD.

In order to reduce the risk of Type 1 errors symptoms were only considered significant when they were significantly more common both in MCI-LB compared with MCI-AD and in DLB compared with AD. Apathy and daytime sleepiness were found to be significantly more common in MCI-LB than MCI-AD but not significantly more common in DLB than AD. These symptoms may develop later in AD than DLB and therefore may still be useful when identifying MCI-LB. This will be tested in independent cohorts.

The 10-point symptom scale was developed and tested in independent samples. As it was developed in a dementia group it may have missed some symptoms that are specific only to the early stages of disease, but it may mean the scale is robust across the early to moderate stages of the disease. This will also be tested in future independent samples.

Unsurprisingly MCI-LB and DLB participants were more likely to be taking levodopa. This may have reduced the difference in reported parkinsonian symptoms between LB and AD groups. It is possible the side-effects of levodopa medication could contribute to other reported symptoms such as confusion. MCI-LB participants were more likely to live with their informant and see them daily. This may have made it more likely for symptoms such as RBD and fluctuations to be detected in this group, as they are rarely reported by the individual themselves. It is possible that such features may have been missed in some of the MCI-AD group.

Participants in the MCI cohort were recruited on the basis of suspected symptoms of Lewy body disease. After a thorough assessment, including a clinical review with a board-certified equivalent psychiatrist, the diagnostic panel found that some of these participants did not

have any Lewy body diagnostic symptom as defined by International Consensus Criteria (McKeith et al. 2005) and fulfilled criteria for MCI-AD. The reported symptom rates of this group may be higher than in a non-selected MCI-AD cohort. Though this may have made differences between the MCI groups more difficult to detect, it increases the robustness of our positive findings. MCI participants had ^{123}I-FP-CIT SPECT imaging to confirm diagnosis; this was only available for dementia participants if it had been carried out as part of their routine clinical care. CSF protein levels were not available.

The diagnosis of MCI-LB has face validity but has not yet been validated against pathological examination. Longitudinal follow-up of these patients will confirm rates of conversion to dementia and their final clinical diagnosis.

Conclusions

The following symptoms are more common in MCI-LB than MCI-AD: fluctuating attention and concentration, unexplained episodes of confusion, rigidity or stiffness in muscles, shuffling walk, change in handwriting, drooling, frequent falls, change in posture, weak voice, symptoms of REM sleep behaviour disorder and difficulty moving around due to misjudging where objects are. Slowness of movement and tremor are commonly reported in AD and MCI-AD and therefore may not be useful symptoms for identifying motor parkinsonism in Lewy body disease. Similarly, though autonomic symptoms and loss of sense of smell are common in LB disease, they are not sufficiently specific to be useful as diagnostic symptoms. Hyposmia and symptoms of RBD may be present for a substantial time prior to the development of cognitive complaints in Lewy body disease.

Acknowledgement

This Research was supported by the NIHR Newcastle Biomedical Research Unit.

The authors would like to thank the Lewy Body Dementia Association for allowing use of the Comprehensive Symptom Checklist.

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Table 1. The Symptom Questionnaire	
Cognitive Symptoms Memory Problem Solving Planning Fluctuating changes in concentration and attention Disorganised speech and conversation Unexplained episodes of confusion **Parkinson's Symptoms** Rigidity or stiffness in muscles Shuffling walk Tremor Slowness of movement Change in Handwriting Slack facial expression Drooling Loss/reduction of sense of smell Balance problems Frequent falls Change in posture Weak voice **Behaviour/mood changes** Seeing things that are not present Hearing things that are not present Depression Apathy (loss of interest and drive) Delusions (false beliefs) Hallucinations in other senses (e.g. touch or smell) Anxiety	**Sleep Symptoms** Troubled by vivid dreams Troubled by nightmares Had involuntary movements of arms and legs Acting out dreams, sometimes violently Cried out during sleep Excessive daytime sleepiness Transient loss of consciousness/unexplained blackouts Insomnia Restless legs syndrome **Autonomic Dysfunction** Dizziness, light-headedness or fainting Sensitivity to heat or cold Urinary incontinence Constipation **Visual Symptoms** Painful/dry eyes Double vision Difficulty reading (because words and letters move around the page) Misjudging objects (have difficulty moving around because you misjudge where objects are) **Perceived response to Cholinesterase Inhibitors/Memantine** Significant improvement Minimal improvement No change Worse

Table 2. Group Demographics							
	Control	MCI-AD	MCI-LB		AD	DLB	
	Mean (SD)	Mean (SD)	Mean (SD)	*p* *MCI-AD v. MCI-LB*	Mean (SD)	Mean (SD)	*p* *AD v. DLB*
n	20	21	36		21	36	
Age	75.9 (7.3)	78.5 (6.4)	75.3 (7.6)	*0.11*	76.3 (6.9)	75.7 (6.3)	*0.71*
Gender (% female)	20	67	33	***0.02***	24	14	*0.47*
MMSE Total	29.1 (0.9)	26.5 (2.1)	26.3 (2.3)	*0.94*	20.5 (4.7)	21.5 (4.6)	*0.49*
AChI (%)	0	24	42	*0.17*	100	97	*1*
Levodopa (%)	0	0	22	***0.02***	0	36	***0.001***
Informant present (%)	-	86	94	0.35	100	100	-
Daily contact with informant (%)	-	57	86	**0.01**	76	92	0.13
Live with informant (%)	-	52	78	**0.047**	71	83	0.33
AChI = On treatment with acetylcholinesterase inhibitor; Levodopa = on treatment with levodopa.							

Table 3. The percentage of patients experiencing each symptom							
	CTRL (%)	MCI-AD (%)	MCI-LB (%)	*P MCI-AD v. MCI-LB*	AD (%)	DLB (%)	*P AD v DLB*
Cognitive Symptoms							
Memory	15	95	94	*1*	100	89	*0.29*
Problem Solving	0	14	36	*0.08*	67	71	*0.77*
Planning	0	29	44	*0.24*	76	80	*0.75*
Fluctuating conc./att.	5	10	39	***0.02***	10	69	***<0.001***
Disorganised speech	0	14	33	*0.12*	10	37	***0.02***
Episodes of confusion	0	0	28	***0.01***	5	54	***<0.001***
Symptoms associated with Parkinson's disease							
Rigidity or stiffness	10	0	28	***0.01***	5	36	***0.01***
Shuffling walk	5	19	53	***0.01***	29	86	***<0.001***
Tremor	20	48	50	*0.86*	48	72	*0.06*
Slowness of movement	0	43	67	*0.08*	43	83	***0.002***
Change in handwriting	35	38	75	***0.01***	38	89	***<0.001***
Slack facial expression	0	0	14	*0.15*	14	54	***0.003***
Drooling	10	10	53	***0.001***	19	80	***<0.001***
Loss of Smell	20	19	44	*0.05*	29	63	***0.01***
Balance problems	13	53	63	*0.46*	40	71	***0.02***
Frequent Falls	0	11	43	***0.02***	5	31	***0.04***
Change in posture	20	29	67	***0.01***	38	82	***0.001***
Weak Voice	7	11	41	***0.02***	5	53	***<0.001***
Neuropsychiatric Symptoms							
Seeing things	5	24	50	*0.05*	5	78	***<0.001***
Hearing things	0	5	11	*0.64*	5	29	***0.04***
Depression	0	14	31	*0.17*	19	22	*1*
Apathy	0	19	47	***0.03***	48	47	*1*
Delusions	0	0	0	*1*	5	17	*0.24*
Other Hallucinations	5	5	11	*0.65*	5	28	***0.04***
Anxiety	5	24	26	*0.83*	19	23	*1*
Sleep Symptoms							
Vivid dreams	5	14	22	*0.73*	5	6	*1*
Nightmares	5	5	22	*0.13*	10	11	*1*
Involuntary movements	10	0	56	***<0.001***	5	54	***<0.001***
Acting out dreams	5	0	50	***<0.001***	0	56	***<0.001***
Crying out	5	19	47	***0.03***	5	64	***<0.001***
Daytime sleepiness	15	29	56	***0.048***	43	64	*0.12*
Transient LOC	0	0	3	*1*	0	3	*1*
Insomnia	20	10	31	*0.10*	25	22	*1*
Restless legs	15	24	25	*0.92*	10	20	*0.46*
Autonomic Symptoms							
Dizziness or Fainting	20	29	47	*0.17*	29	53	*0.08*
Sensitivity to heat or cold	30	52	64	*0.39*	48	57	*0.49*

Urinary Incontinence	5	29	28	*0.95*	29	26	*0.82*
Constipation	25	38	44	*0.64*	10	53	***0.001***
Visual Symptoms							
Dry/painful eyes	35	33	38	*0.71*	14	25	*0.50*
Double Vision	5	10	18	*0.70*	5	36	***0.01***
Difficulty reading	5	0	18	*0.07*	5	17	*0.24*
Misjudging Objects	5	0	35	***0.002***	19	58	***0.004***
CTRL=Control; conc./att.=concentration/attention; LOC-loss of consciousness							

Table 4. Median duration of key symptoms in MCI-LB and DLB groups at baseline assessment		
	MCI-LB (yrs)	DLB (yrs)
Memory problems	3.0	4.0
Fluctuating Att./Conc.	1.5	2.0
Episodes of confusion	1.0	2.0
Rigidity/stiffness	4.0	2.0
Shuffling walk	1.8	1.5
Slowness of movement	2.0	2.0
Change in handwriting	1.0	1.5
Drooling	0.6	1.0
Loss of smell	17.0	10.0
Frequent falls	1.5	1.5
Change in posture	1.0	2.0
Weak voice	2.0	2.0
Seeing things not present	2.0	2.0
Involuntary movements	2.3	10.0
Acting out dreams	3.0	7.8
Cried out during sleep	4.5	5.5
Misjudging Objects	2.0	1.3

Table 5. Symptoms present in >50% of DLB and <20% of AD cases
Fluctuating conc./att.
Episodes of confusion
Slack facial expression
Drooling
Weak Voice
Seeing things not present
Involuntary movements
Acting out dreams
Crying out during sleep
Misjudging Objects