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FEATURED ARTICLE

# The temporal onset of the core features in dementia with Lewy bodies

**Parichita Choudhury**[1] | **Jonathan Graff-Radford**[1] | **Jeremiah A. Aakre**[2] | **Lincoln Wurtz**[1] | **David S. Knopman**[1] | **Neill R. Graff-Radford**[3] | **Kejal Kantarci**[4] | **Leah K. Forsberg**[1] | **Julie A. Fields**[5] | **Otto Pedraza**[6] | **Qin Chen**[4,7] | **Toji Miyagawa**[1] | **Gregory S. Day**[3] | **Philip Tipton**[3] | **Rodolfo Savica**[1] | **Hugo Botha**[1] | **Christian Lachner**[6] | **Brynn Dredla**[3] | **R. Ross Reichard**[8] | **Ronald C. Petersen**[1] | **Dennis W. Dickson**[9] | **Bradley F. Boeve**[1] | **Tanis J. Ferman**[6]

[1] Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA

[2] Department of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota, USA

[3] Department of Neurology, Mayo Clinic, Jacksonville, Florida, USA

[4] Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA

[5] Department of Psychiatry and Psychology, Mayo Clinic, Rochester, Minnesota, USA

[6] Department of Psychiatry and Psychology, Mayo Clinic, Jacksonville, Florida, USA

[7] Department of Neurology, West China Hospital of Sichuan University, Sichuan, China

[8] Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA

[9] Department of Neuroscience, Mayo Clinic, Jacksonville, Florida, USA

**Correspondence**
Tanis J. Ferman, Dept of Psychiatry and Psychology, Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL 32224, USA.
E-mail: ferman.tanis@mayo.edu

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## Abstract

**Introduction:** We examined the temporal sequence of the core features in probable dementia with Lewy bodies (DLB).

**Methods:** In 488 patients with probable DLB, the onset of each core feature and time to diagnosis was determined for men and women, and a pathologic subgroup (n = 209).

**Results:** REM sleep behavior disorder (RBD) developed before the other core features in men and women. Men were more likely to have RBD and were diagnosed with probable DLB earlier than women. Visual hallucinations developed after the other core features in men, but in women, they appeared earlier and concurrently with fluctuations and parkinsonism. Women were older and more cognitively impaired at first visit, were less likely to have RBD, more likely to be diagnosed with probable DLB later than men, and more likely to have neocortical tangles.

**Discussion:** An earlier latency to probable DLB was associated with men, RBD, and Lewy body disease without neocortical tangles.

KEYWORDS
Alzheimer's disease, Lewy body disease, neuropsychiatric, sex

## 1 | INTRODUCTION

Dementia with Lewy bodies (DLB) is a progressive neurodegenerative condition characterized by cognitive impairment and varying combinations of four core features that include REM sleep behavior disorder (RBD), parkinsonism, fluctuating cognition, and fully formed visual hallucinations (VH).[1] The pathologic hallmark of DLB is Lewy-related pathology, but at least half of patients with DLB in autopsy samples have differing degrees of co-existing Alzheimer's disease (AD)-related pathology.[2–6] Since the addition of RBD to the clinical criteria, the diagnostic sensitivity of DLB has improved to 85%,[7] albeit higher for Lewy body disease without neocortical neurofibrillary tangles, and lower for those with widespread neocortical tangles.[3] Despite greater awareness of DLB and the availability of structured diagnostic tools,[8,9] it is not uncommon for the identification of DLB to be delayed,[10,11] or go unrecognized.[12,13] This has major implications for patient care,[14,15] and also for the design and implementation of clinical trials.[16]

Establishing a diagnosis of clinically probable DLB requires two or more core features and depends on when each core feature declares itself. RBD is a prodromal feature that often develops before the onset of dementia and other core features.[17–19] In clinical settings, men are more likely to have a reported history of RBD,[17,20] and Lewy body disease without neocortical tangles.[2,3,21–23] However, not all patients with DLB develop RBD, and patients with mixed pathology have lower rates of RBD[24,25] and a longer latency from cognitive onset to DLB diagnosis.[3] It is not known if men and women differ in the order of appearance of the core features or in the timing of when probable DLB criteria is met. The goal of this study was to characterize the temporal sequence of the core features in men and women with probable DLB, and to determine whether sex, RBD status, and pathology were associated with an earlier or later diagnosis of probable DLB in our clinical cohort and autopsied subset.

## 2 | METHODS

### 2.1 | Study participants

Participants from the Mayo Clinic Alzheimer's Disease Research Center (ADRC) seen between January 1998 and December 2019 were included if the patient had a reliable informant and clinical criteria for probable DLB[1] was met by the last evaluation. Clinically probable DLB was defined as dementia with two or more of the following core features: probable RBD, spontaneous parkinsonism, fully formed VH, and fluctuating cognition or arousal. Patients were excluded if the parkinsonism preceded the onset of cognitive symptoms by more than a year, satisfying the "1 year rule" of Parkinson's disease dementia.[26]

#### 2.1.1 | Standard protocol approval and patient consents

The study was approved by the Mayo Clinic Institutional Review Board and followed the Health Insurance Portability and Accountability Act (HIPAA) guidelines. Participants and their legally authorized representatives provided written informed consent.

### 2.2 | Procedures

For each visit, all participants underwent comprehensive neurologic and neurocognitive evaluations. At each visit, the clinician obtained information regarding each core feature's presence or absence along with the month and year of onset by clinical interview with the patient and informant. The estimated onset of cognitive symptoms referred to the month and year when cognitive difficulties became apparent to the informant. VH were required to be fully formed and recurrent. Clinically probable RBD required informant report of a history of recurrent episodes of dream enactment behavior during sleep with movements that appeared to match dream content. Parkinsonism was based on neurologic examination and onset was determined (or confirmed) by the neurologist at each visit. The 13-item version of the Unified Parkinson's Disease Rating Scale was used to estimate parkinsonism severity,[27] but was not used for diagnosis and was only available for 464 patients. Fluctuating cognition was determined by both clinical observation of the patient and specific inquiry with the informant about obvious variability in the patient's attention, alertness, communication, and daily functioning. Given the time frame of data collection, the four-item Mayo Fluctuations Scale (MFS)[28] was not available at every visit, but in 401 patients, there was 83% agreement between clinician determination of fluctuations and at least one visit with an MFS fluctuations score $\geq 3$. Dementia severity was based on a non-cognitive rating from the Global Deterioration Scale (GLDS),[29] and from cognitive assessment using the Mini-Mental State Examination (MMSE) and the Mattis Dementia Rating Scale (DRS). A consensus meeting of neurologists and neuropsychologists was held after each visit that rendered a clinical diagnosis based on established criteria. We calculated the patient's age when two or more core features developed, and the latency in years from estimated cognitive onset to the emergence of two or more core features.

### 2.3 | Neuropathologic examination

Brains were sampled using a standardized protocol with macroscopic and microscopic evaluations. Paraffin embedded tissue sections were

cut at 5-$\mu$m thickness, and mounted on glass slides for histopathologic and immunohistochemical studies. All cases underwent immunohistochemistry for $\alpha$-synuclein (LB500, 1:1000, mouse monoclonal antibody [Invitrogen] or NACP, 1,3000, rabbit polyclonal; Mayo Clinic's antibody). Neurofibrillary tangles (NFT) were identified using thioflavin-S immunohistochemistry or Bielschowsky silver stain. Braak NFT stage was determined based on the distribution of NFTs and operationally defined as follows: Stage 0 had no NFTs, Stage I had NFTs confined to the transentorhinal cortex, Stage II had NFTs in the entorhinal cortex, Stage III had NFTs in the hippocampus, Stage IV had NFTs in the isocortex of the temporal lobe, Stage V had NFTs in the association cortices, and Stage VI had NFTs in the primary visual cortex.[30] Classification of Lewy body disease included brainstem-predominant Lewy body disease (BLBD);[31] Alzheimer's disease with amygdala-predominant Lewy body disease (AD-ALB);[32] transitional brainstem and limbic Lewy body disease (TLBD); and diffuse brainstem, limbic, and neocortical Lewy body disease (DLBD).[1] The TLBD and DLBD groups were further distinguished by the absence or presence of neocortical NFTs classified by a low (L) Braak stage of 0 to III or a high (H) Braak stage of IV to VI, respectively. This classification included the four pathologic subgroups of TLBD-L, DLBD-L, TLBD-H, and DLBD-H, with 83% overlap with our prior pathology study.[3]

**RESEARCH IN CONTEXT**

1. **Systematic review**: We reviewed published literature regarding probable dementia with Lewy bodies (DLB). Little is known about the order of appearance of the core features in men and women, and whether subgroups harbor an earlier or later emergence of the core features required for a diagnosis of probable DLB.
2. **Interpretation**: In our cohort, probable REM sleep behavior disorder (RBD) was more common in men, but preceded the other core features in both men and women. Visual hallucinations were more common in women, and were more likely to develop after the other core features in men. Patients without RBD were older and more impaired at the initial visit, had a longer latency to probable DLB, and were more likely to have neocortical tau pathology.
3. **Future directions**: Further study is needed to examine whether other clinical symptoms emerge early in DLB, and whether subgroups can be distinguished by quantitative indicators of pathologic burden.

### 2.4 | Statistical analysis

Categorical variables were summarized using percentages and compared using Chi-square tests. Continuous variables were summarized using means with standard deviations, or medians with interquartile range. Nonparametric analyses were carried out using the Mann-Whitney U-test for two independent groups, Kruskal-Wallis for more than two independent groups, and Wilcoxon rank-sum test for paired group comparisons. Cumulative frequency distributions of the onset age of each core feature, and the time from estimated cognitive symptom onset to each core feature, were plotted for men and women. To compare the distribution curves, the Peto-Peto generalization of the Wilcoxon test was carried out. Given the exploratory nature of this study, statistical significance was set at a *P*-value of .01. All analyses were conducted using statistical software (SAS version 9.4, SPSS version 25).

## 3 | RESULTS

### 3.1 | Characterization of the cohort

Our cohort of clinically probable DLB included 488 patients with a mean follow-up of 3.8 ± 3.0 years from the initial clinical visit (Table 1). Patients were disproportionately male (76%), White (95%), and had a mean education of 14.6 ± 3.2 years. Baseline GLDS scores ranged from 2 to 6 and included mild cognitive impairment in 18%, mild dementia in 34%, mild to moderate dementia in 28%, moderate dementia in 16%, and moderate to severe dementia in 4%. Last visit GLDS scores ranged from 3 to 7 and dementia severity was mild in 15%, mild to moderate in 16%, moderate in 22%, moderate to severe in 37%, and severe in 10%. Of the 409 deaths, time from estimated cognitive onset to death showed no sex difference (Table 1; $P = .47$) and the interval from last visit to death was a mean of 1.7 ± 1.8 years with no sex difference ($P = .25$).

The cohort included 28% with two core features, 33% with three core features, and 39% with four core features. Table 1 shows that parkinsonism was a frequent core feature for men and women, RBD was more common in men ($P < .001$), VH were more common in women ($P = .001$), and fluctuations showed no sex difference ($P = .43$). There were no significant associations between the core features (i.e., hallucinators were not more likely to have RBD, parkinsonism, or fluctuations). Each core feature was examined in relation to the timing of the other core features, and RBD was the only core feature associated with onset age and latency from cognitive onset to the other core features (Table 1).

By the estimated onset of cognitive symptoms, 55% of 488 patients already had RBD (63% men vs. 30% women, $P < .001$). Of the 372 patients with a history of RBD, this feature started five or more years before the cognitive symptoms in 36%, and at least a decade earlier in 20%. By the time cognitive symptoms started, 28% of 488 had fluctuations (29% men vs. 26% women, $P = .58$), 25% had parkinsonism (26% men vs. 21% women, $P = .27$), and 12% of patients had VH (9% men vs. 22% women, $P < .001$).

Treatment with cholinesterase inhibitors was documented in 88%, with no difference between core features, or between men and women. Of the 433 with parkinsonism, 32% were treated with carbidopa-levodopa and 7% with a dopamine agonist. Parkinsonism

**TABLE 1** Demographic and clinical features of clinically probable DLB cohort

| Variable | Cohort | Men | Women | Men vs. Women *P* | RBD | No RBD | RBD vs. no RBD *P* |
|---|---|---|---|---|---|---|---|
| N | 488 | 370 | 118 | – | 372 | 116 | – |
| Age at first visit | 73 [68,78] | 72 [67, 78] | 75 [71, 78] | 0.012 | 72 [67, 77] | 76 [71, 80] | <0.001 |
| Baseline MMSE score | 25 [21, 27] | 25 [21, 27] | 24 [20, 26] | 0.005 | 25 [22, 27] | 23 [20, 26] | 0.001 |
| Baseline DRS scores | 124 [112, 132] | 126 [113, 133] | 120 [108, 129] | 0.001 | 126 [113, 133] | 118 [108, 126] | <0.001 |
| DLB core features | | | | | | | |
| RBD | 372 (76%) | 311 (84%) | 61 (52%) | <0.001 | – | – | – |
| Parkinsonism | 433 (89%) | 335 (91%) | 98 (83%) | 0.025 | 335 (90%) | 98 (84%) | 0.09 |
| Fluctuations | 373 (76%) | 286 (77%) | 87 (74%) | 0.43 | 280 (75%) | 94 (81%) | 0.22 |
| Visual hallucinations | 341 (70%) | 244 (66%) | 97 (82%) | 0.001 | 262 (70%) | 80 (69%) | 0.88 |
| Last UPDRS score | 13 [7, 19] | 13 [8, 20] | 11 [3,17] | 0.004 | 13 [7,30] | 12 [5, 18] | 0.030 |
| Onset age | | | | | | | |
| Cognitive symptoms | 70 [65, 75] | 70 [64, 75] | 72 [67, 76] | 0.013 | 69 [64, 74] | 73 [68, 78] | <0.001 |
| RBD | 65 [56, 72] | 64 [56, 72] | 68 [61, 75] | 0.008 | 65 [57, 72] | – | – |
| Parkinsonism | 73 [67, 78] | 72 [67, 77] | 75 [69, 78] | 0.002 | 71 [66, 76] | 76 [71, 80] | <0.001 |
| Fluctuations | 73 [67, 77] | 72 [66, 77] | 75 [69, 79] | 0.011 | 71 [66, 76] | 75 [70, 80] | <0.001 |
| Visual hallucinations | 73 [68, 78] | 73 [67, 78] | 76 [70, 79] | 0.028 | 72 [67, 77] | 76 [72, 80] | <0.001 |
| ≥ 2 core DLB features | 72 [67, 77] | 71 [66, 76] | 74 [69, 78] | 0.001 | 70 [65, 76] | 76 [72, 80] | <0.001 |
| Time from cognitive onset | | | | | | | |
| to RBD | -1.3 [-8.0, 0.5] | -2.0 [-9.0, 0.0] | 0.0 [-2.0, 2.0] | 0.001 | -1.3 [-8.0, 0.5] | – | – |
| to parkinsonism | 1.9 [0.0, 4.0] | 1.5 [0.0, 3.5] | 2.1 [0.0, 5.0] | 0.014 | 1.6 [0.0, 3.9] | 2.3 [0.4, 5.0] | 0.004 |
| to fluctuations | 1.0 [0.1, 3.8] | 1.0 [0.0, 3.8] | 1.5 [0.0, 3.8] | 0.68 | 1.0 [0.0, 3.8] | 1.0 [0.0, 3.6] | 0.62 |
| to visual hallucinations | 2.8 [1.0, 4.8] | 3.0 [1.0, 5.0] | 2.0 [0.0, 4.0] | 0.014 | 2.8 [1.0, 4.5] | 3.0 [1.0, 5.0] | 0.58 |
| to ≥ 2 core DLB features | 1.0 [0.0, 3.4] | 1.0 [0.0, 3.3] | 2.0 [0.0, 4.0] | 0.005 | 1.0 [0.0, 3.0] | 2.8 [0.5, 5.1] | <0.001 |
| Deceased | | | | | | | |
| Deaths | 409 (84%) | 300 (81%) | 109 (92%) | – | 299 (80%) | 110 (95%) | – |
| Death age | 79 [74, 85] | 79 [73, 84] | 81 [76, 86] | 0.008 | 78 [73, 83] | 82 [77, 86] | <0.001 |
| Cognitive onset to death | 8.2 [6.2, 10.6] | 8.1 [6.2, 10.6] | 8.6 [6.4, 10.8] | 0.47 | 8.0 [6.2, 10.5] | 8.7 [6.6, 10.7] | 0.17 |

Abbreviation: DLB: dementia with Lewy bodies, DRS: Mattis Dementia Rating Scale, MMSE: Mini-Mental State Examination, RBD: rapid eye movement (REM) sleep behavior disorder; UPDRS, Unified Parkinson's Disease Rating Scale.
Notes: Values represent n (%) and median years [25th and 75th percentile quartiles]. UPDRS was available for 358 men and 106 women, and for 363 with RBD and 101 without RBD. Cognitive onset to death refers to time from the month/year of estimated cognitive symptom onset to month/year of death.

severity at the last evaluation was greater for men than women (Table 1, $P = .004$). Treatment for parkinsonism was more common in men (41% men vs. 22% women, $P < .001$) and was not associated with VH, or time from cognitive onset to VH for either men or women.

## 3.2 | Age of onset of cognitive symptoms and core features

The median onset ages of each core feature are provided in Table 1 and the cumulative frequencies of each core feature across onset age are plotted in Figure 1.

When men were examined separately, parkinsonism, fluctuations, and VH showed a steeper age-related increase than RBD ($P < .001$; Figure 1A). In men, RBD emerged at a younger median age than the cognitive symptoms, parkinsonism, fluctuations, or VH ($P < .001$; Table 1). Cognitive symptoms also developed at a younger median age than parkinsonism, fluctuations, or VH ($P < .001$). Parkinsonism and fluctuations in men did not differ in median onset age ($P = .63$), and VH emerged at an older median age than each of the other DLB features ($P < .001$).

For women, the cumulative frequency distributions showed a steeper age-related increase for the cognitive symptoms compared to each of the core DLB features ($P < .001$; Figure 1B). Women developed RBD and cognitive symptoms at similar median ages ($P = .56$; Table 1), each of which developed at a younger median age than parkinsonism, fluctuations, or VH ($P < .001$).

At the initial visit, women were older than men ($P = .012$) and had overall lower cognitive scores ($P \leq .005$; Table 1). Women were also older when two or more core features (probable DLB) emerged

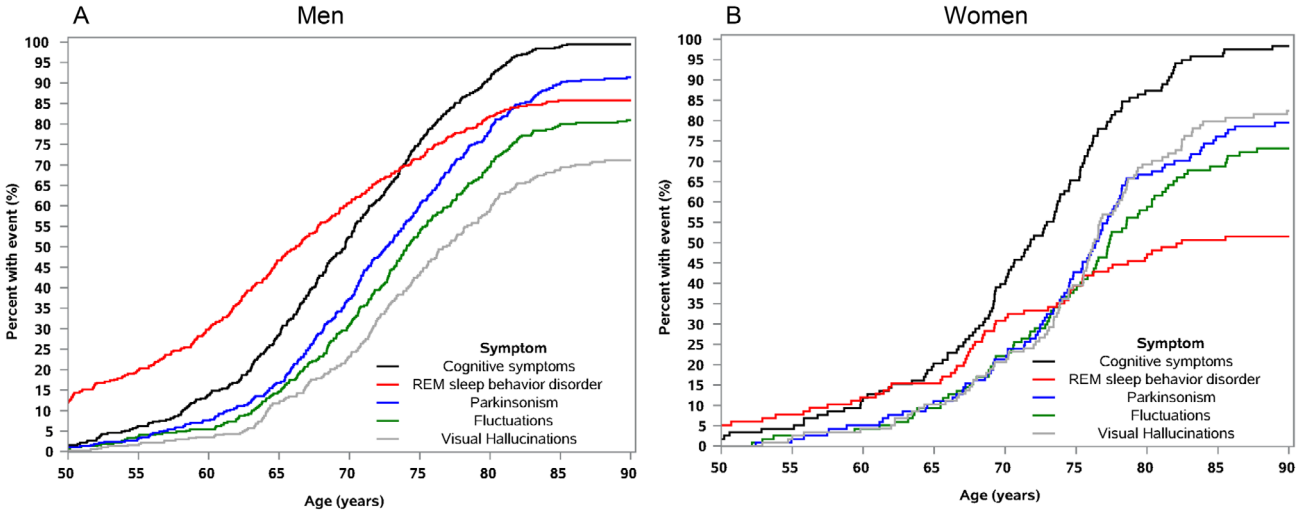


**FIGURE 1** Cumulative frequency of the onset age for each of the four core features of dementia with Lewy bodies (DLB); (A) represents men (n = 370) and (B) represents women (n = 118)

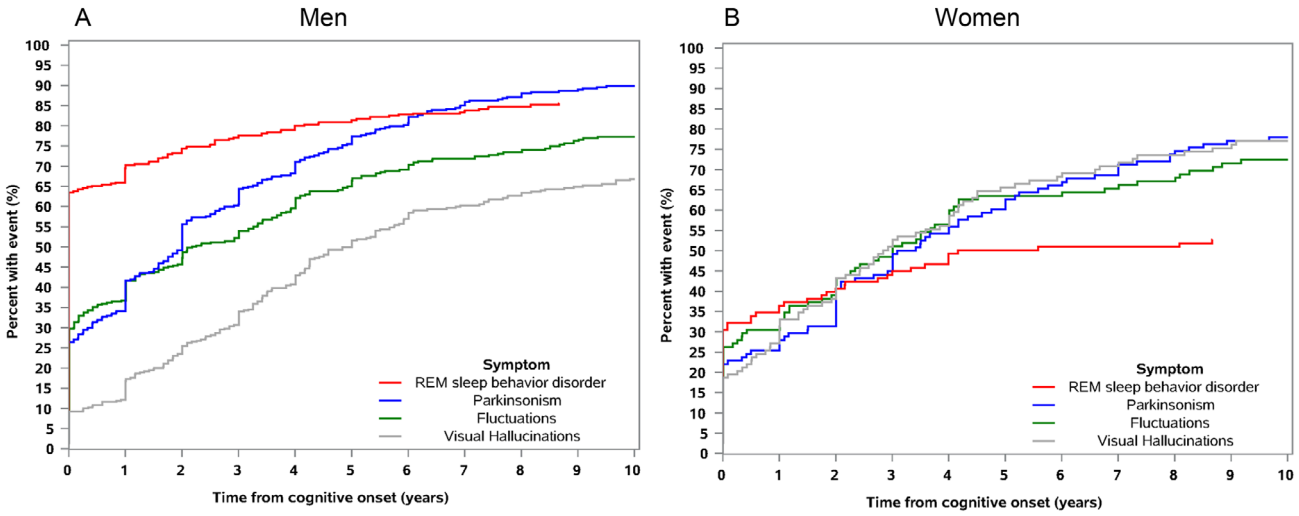


**FIGURE 2** Cumulative frequency of time from cognitive onset to each of the four core features of dementia with Lewy bodies (DLB); (A) represents men (n = 370) and (B) represents women (n = 118)

(*P* = .001) and older at death (*P* = .008). These differences were also associated with RBD status (*P*≤.001; Table 1), but with no sex differences in those with RBD, or in those without RBD.

## 3.3 | Time to each core feature from cognitive symptom onset

The median latencies to each core feature are provided in Table 1 and the cumulative frequencies of the time to each core feature from cognitive onset are plotted in Figure 2.

In men, RBD was more likely to develop by the time of cognitive onset and then showed a slower rate of increase in the time from cognitive onset compared to the other core features (*P* < .001; Figure 2A). Across the core features, median latencies from cognitive symptom onset in men were shortest for RBD (*P* < .001), longest for VH (*P* < .001), and the intermediate values did not differ between parkinsonism and fluctuations (*P* = .42).

In women, the curves representing the cumulative frequencies across time from cognitive onset to each core feature showed overlap (Figure 2B). There was a trend for the percentage with RBD to plateau while rates of fluctuations, parkinsonism, or VH continued to increase. Like men, women exhibited a shorter median latency to RBD than each of the other core features (*P* < .001), but unlike men, women developed VH within the same temporal window as parkinsonism (*P* = .24) and fluctuations (*P* = .36).

RBD emerged earlier in the disease course for men than women (*P* = .001: Table 1) and was more likely to precede cognitive symptoms by 5 years or more in men (39% men vs. 18% women; *P* = .002). By a smaller margin, the median time to VH from cognitive onset was earlier in women (*P* = .014) and the median time to parkinsonism was earlier in men (*P* = .014).

Men had a shorter latency from cognitive onset to meeting criteria for probable DLB than women ($P = .005$; Table 1), but RBD was also associated with a shorter latency to probable DLB (Table 1; $P < .001$). Upon further examination, women with RBD were just likely as men with RBD to exhibit a short latency to probable DLB ($P = .40$), and men without RBD were just as likely as women without RBD to exhibit a longer latency ($P = .46$).

### 3.4 | Autopsy diagnoses and temporal onset of DLB

In our cohort of clinically probable DLB, Lewy body disease was found in 189 (90%) of the 209 patients who underwent autopsy (Table 2). This included 84% with TLBD or DLBD, 1% with BLBD, and 5% with AD-ALB.[32] Of the 20 patients without Lewy-related pathology, 18 (9%) had AD (11/18 with comorbid cerebrovascular disease), 1 (0.5%) had progressive supranuclear palsy (PSP), and 1 (0.5%) had Creutzfeldt-Jakob disease (CJD). The autopsied sample had a mean follow-up from initial to last visit of 4.8 ± 3.2 years, which was longer than 3.0 ± 2.6 years for the remainder of the cohort ($P < .001$).

In the autopsied subset, 30% had two core features, 26% had three core features, and 44% had four core features. RBD was more common in men (79% men vs. 40% women, $P < .001$), but there was no sex difference in parkinsonism (89% men vs. 88% women, $P = .83$), fluctuations (83% men vs. 79% women, $P = .51$), or VH (74% men vs. 79% women, $P = .43$).

The onset age and order of appearance of each core feature for men and women in the autopsy subset showed the same patterns as the clinical cohort (Figures 1 and 2). Also, in the autopsy subset, criteria for probable DLB was met at a younger median age and at a shorter median latency from cognitive onset in men and in those with RBD, with the same median values as the clinical cohort provided in Table 1.

We examined four pathologic subgroups of Lewy body disease distinguished by the distribution of α-synuclein and neocortical tau pathology (TLBD-L, DLBD-L, DLBD-H, TLBD-H).[3] The TLBD and DLBD groups without neocortical tangles (TLBD-L and DLBD-L) were disproportionately male, while DLBD-H and TLBD-H showed more comparable male and female representation (Table 2). RBD was more common in TLBD-L and DLBD-L than in DLBD-H, and more common in DLBD-H than in either TLBD-H or AD. Onset age of probable DLB was younger for patients with TLBD-L, DLBD-L, and DLBD-H than those with TLBD-H or AD ($P = .001$). The latency to probable DLB from cognitive onset was shortest for TLBD-L and DLBD-L (median < 1 year), which was shorter than DLBD-H (median 2 years; $P = .014$), each of which were shorter than TLBD-H (median 7.3 years; $P < .001$) and AD (median 4.6 years; $P = .001$; Table 2). In the DLBD-H subgroup, men and women did not differ in the age when criteria for probable DLB was met ($P = .58$) or in the latency to probable DLB ($P = .09$). Like the clinical cohort, in the DLBD-H subgroup, RBD was associated with a younger age to probable DLB ($P = .003$) and a shorter latency to probable DLB from cognitive onset ($P < .001$).

## 4 | DISCUSSION

In our longitudinal cohort of 488 patients with a clinical diagnosis of probable DLB, men were disproportionately represented, a pattern found in other centers.[2,12,33] We examined each core feature's order of appearance in terms of onset age (Figure 1) and time from cognitive onset (Figure 2). For both men and women, RBD was the earliest core feature to develop and it emerged before the other core features of parkinsonism, fluctuations, and VH (Figure 3). In addition, RBD became apparent at a younger age in men compared to women.[34,35] Men were also more likely to develop RBD before the onset of cognitive symptoms, while women were more likely to develop RBD and cognitive symptoms within the same time frame. This adds to the established evidence that RBD is an early harbinger of DLB[17,18,20,36] but also suggests that men may have a longer preclinical interval before the cognitive symptoms develop. If so, men may have a wider window of opportunity for intervention than women, when future targeted therapies become available.

Compared to men, women met clinical criteria for probable DLB at an older age and after a longer latency from cognitive onset. This was related to RBD, the only core feature that was associated with a later diagnosis of probable DLB when absent, and with an earlier diagnosis when present. Moreover, RBD was less common than each of the other three core features in women. Only half of the women in our cohort reported a history of RBD compared to 84% of the men. This sex difference in RBD has been frequently observed in clinical settings, even though the population prevalence of RBD may be similar in women and men.[37] If the motor activity during REM sleep is more vigorous in men,[38,39] then it is possible that RBD may be noticed earlier in men. The underlying pathophysiology for such a difference is not understood, but increased REM sleep-phasic muscle activity in men,[40–42] and sex differences in the types of motor movements[40] may be contributing factors. Although RBD is a strong predictor of probable DLB,[17,18,36] it is possible that a more subtle expression of RBD, perhaps more common in women, may be under-reported or unrecognized without routine polysomnography.

At the initial visit, women were older and more cognitively impaired than men. It is unclear why women may present for care at a later stage of the disease, but this was also observed in a large Amsterdam cohort.[43] Clarification of the characteristics that prompt patients to seek care is needed because delays in the diagnosis of DLB may place patients at greater risk for exposure to medications with greater iatrogenic risk, such as anticholinergic agents and certain neuroleptics.[1]

In our clinical cohort of probable DLB, women were more likely than men to have VH, a difference that was not related to the use of anti-parkinsonian agents. In addition, women were older when they developed VH and were more likely to develop VH earlier in the disease course and as an initial feature, compared to men. While a sex difference in VH and its association with older age in women has been reported by others,[43,44] whether this translates to VH being a common prodromal pathway for women with DLB has yet to be determined. Nonetheless, a sex difference in VH has not been consistently found in

**TABLE 2** Core features and pathologic subgroups in 209 autopsied cases

| | TLBD-L | DLBD-L | DLBD-H | TLBD-H | AD | *P* | AD-ALB | BLBD | PSP | CJD |
|---|---|---|---|---|---|---|---|---|---|---|
| N | 30 | 47 | 78 | 21 | 18 | – | 10 | 3 | 1 | 1 |
| Male | 28 (93%)[a] | 40 (85%)[a] | 50 (64%)[b] | 13 (62%)[b] | 12 (67%)[b] | 0.005 | 7 (70%) | 1 (33%) | 1 (100%) | 0 (0%) |
| Core features | | | | | | | | | | |
| RBD | 27 (90%)[a] | 41 (87%)[a] | 53 (68%)[b] | 8 (38%)[c] | 5 (28%)[c] | <0.001 | 5 (50%) | 1 (33%) | 0 (0%) | 1 (100%) |
| Parkinsonism | 28 (93%) | 42 (89%) | 68 (87%) | 20 (95%) | 15 (83%) | 0.68 | 7 (70%) | 3 (100%) | 1 (100%) | 1 (100%) |
| Fluctuations | 26 (87%) | 40 (85%) | 66 (85%) | 15 (71%) | 13 (72%) | 0.42 | 8 (80%) | 1 (33%) | 1 (100%) | 0 (0%) |
| VH | 21(70%) | 39 (83%) | 58 (74%) | 15 (71%) | 11 (61%) | 0.41 | 8 (80%) | 3 (100%) | 1 (100%) | 1 (100%) |
| Onset age | | | | | | | | | | |
| Cognitive | 68 [63, 74] | 69 [63, 74] | 69 [63, 75] | 71 [65, 75] | 71 [68, 76] | 0.43 | 68 [63, 73] | 76,81,81 | 66 | 74 |
| RBD | 61 [46, 68] | 62 [56, 70] | 67 [60, 72] | 61 [56, 77] | 68 [45, 79] | 0.22 | 60 [59, 71] | 78 | – | 74 |
| Parkinsonism | 69 [65, 74][a] | 71 [64, 77][a] | 72 [67, 77][a] | 76 [74, 82][b] | 76 [72, 81][b] | 0.001 | 71 [65, 78] | 81,84,84 | 69 | 75 |
| Fluctuations | 71 [65, 78] | 72 [65, 76] | 71 [67, 77] | 73 [65, 82] | 76 [72, 79] | 0.43 | 71 [67, 78] | 81 | 67 | 74 |
| VH | 72 [65, 77] | 72 [65, 77] | 72 [67, 78] | 76 [72, 80] | 76 [73, 79] | 0.20 | 72 [71, 79] | 82,83,84 | 72 | 74 |
| ≥ 2 core DLB features | 69 [64, 74][a] | 70 [65, 74][a] | 71 [66, 77][a] | 76 [70, 81][b] | 77 [72, 81][b] | 0.001 | 72 [64, 77] | 81,82,83 | 68 | 74 |
| Time from cognitive onset | | | | | | | | | | |
| to RBD | -5.8 [-12.0, -1.0] | -0.5 [-9.0, 0] | -1.0 [-6.9, 1.0] | 2.0 [-11.3, 6.8] | 0 [-10.5, 2.5] | 0.061 | 0.5 [-10.4, 3.0] | -3.0 | – | 0.5 |
| to parkinsonism | 1.0 [0, 3.3][a] | 1.0 [0, 2.5][a] | 2.5 [0.3, 4.4][a] | 6.2 [3.6, 10.3][b] | 4.4 [2.0, 8.5][b] | <0.001 | 4.1 [1.8, 5.0] | 0, 3.3, 8 | 2 | 1.5 |
| to fluctuations | 1.5 [0, 3.6] | 1.0 [0, 3.6] | 1.0 [0, 3.6] | 3.8 [0, 10.0] | 3.0 [2.2, 6.0] | 0.023 | 3.4 [0.7, 4.8] | 0 | 1 | – |
| to VH | 3.3 [0.8, 6.5] | 2.8 [0.4, 4.5] | 2.8 [1.1, 4.1] | 6.8 [3.3, 10.0] | 3.0 [2.0, 5.1] | 0.020 | 5.5 [2.0, 9.0] | 1, 1.8, 8 | 6.1 | 0.5 |
| ≥ 2 core DLB features | 0.1 [0, 3.1][a] | 0.1 [0, 2.2][a] | 2.0 [0, 3.7][b] | 7.3 [3.2, 10.3][c] | 4.6 [3.0, 7.5][c] | <0.001 | 3.4 [1.8, 4.3] | 0, 1, 8.3 | 2 | 0.5 |
| to death | 8.1 [6, 12] | 8.5 [7, 11] | 8.3 [7, 10] | 12.2 [8, 15] | 9.6 [7, 15] | 0.071 | 10.2 [8, 12] | 7, 10, 12 | 8 | 4.5 |

Abbreviation: AD, Alzheimer's disease; AD-ALB, Alzheimer's disease with amygdala-predominant Lewy bodies; BLBD: brainstem-predominant Lewy body disease; CJD, Creutzfeldt-Jakob disease; DLB, dementia with Lewy bodies; DLBD, diffuse Lewy body disease; H, Braak NFT stage IV to VI categorized as high; L, Braak NFT stage 0 to III categorized as low; NFT, neurofibrillary tangles; PSP, progressive supranuclear palsy; RBD, REM sleep behavior disorder; TLBD, transitional Lewy body disease; VH, visual hallucinations.

Notes: Values represent n (%), median years [25% and 75% percentiles], and individual values in cells with sample sizes of three or less.

For Kruskal-Wallis comparisons with *P*-value < .01, different letter superscripts ([a-c]) represent post hoc paired comparisons of $P < .05$.

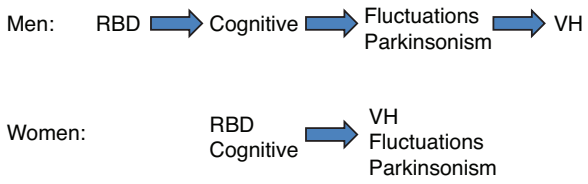


**FIGURE 3** Illustration of the temporal sequence of each core DLB feature based on comparisons of median onset age and median latency from cognitive onset in men and women. Features to the right of each arrow represent older median onset ages and longer median latencies from cognitive onset compared to features to the left of each arrow ($P < .001$). Stacked features do not differ in median onset age or median latency from cognitive onset. DLB, dementia with Lewy bodies; RBD, REM sleep behavior disorder, VH, visual hallucinations [Correction added on December 21, 2021, after first online publication: In the initial publication of this article, the word "Parkinsonism" was omitted from the "Men" line in Figure 3. The word has now been added under "Fluctuations".]

other studies,[45,46] and was no longer significant in our autopsy subset where the gap narrowed between men and women with VH. For our autopsy subgroup, this appeared related, in part, to longer follow-up and the later onset of VH in men, but it is also possible that sampling differences may exist between the clinical cohort and those who agree to autopsy. Despite these distinctions, the clinical cohort and autopsy subset showed that VH were more likely to emerge after the other core features in men, while women did not demonstrate this time lag (Figure 3).

Men and women showed similar rates of parkinsonism and fluctuations, and these features showed similar latencies from cognitive onset (Figure 3). The women in our cohort had less overall parkinsonism severity than men, but whether there are sex differences in motor phenotype or in rates of motor progression in DLB analogous to that reported in Parkinson's disease warrants further study.[47,48] Also, women were less likely to be treated for parkinsonism, and it is not known if women may be at greater risk for under-treatment of motor symptoms when the VH and parkinsonism develop within the same time frame.

In our cohort of clinically probable DLB, RBD was a common prodromal feature that was present by the time of cognitive onset in half the sample. Parkinsonism and fluctuations developed preclinically in about a quarter of the sample, and 12% developed VH by the time cognitive symptoms became apparent. This adds to the evidence that parkinsonism,[45,49] RBD,[50] fluctuations,[51] and VH[52] each have the potential to develop as an initial or pre-dementia feature of DLB,[53] consistent with the recently published research criteria for the diagnosis of prodromal DLB.[54] Studies that follow patients with idiopathic RBD provide evidence that mild cognitive and motor changes often begin years before phenoconversion to probable DLB,[33,50] but less is known about the prodromal stages of DLB in those without RBD.

Of the patients with probable DLB who came to autopsy, 84% had TLBD or DLBD, of whom 56% had co-existing neocortical neurofibrillary tangle pathology (Table 2), consistent with previous studies.[3,55,56] The timing of the core features examined separately in men and women was consistent with the larger clinical cohort (Figures 1–3). As with other studies, patients with Lewy body disease and a low tangle stage were more likely to be men and individuals with RBD.[3,13,24] Moreover, women were less likely to have RBD[13] and more likely to have Lewy body disease with co-existing neocortical tangles.[22,23]

The time to probable DLB from cognitive onset was shortest for Lewy body disease without neocortical tangles (TLBD-L, DLBD-L), intermediate for diffuse Lewy body disease with neocortical tangles (DLBD-H), and longest for transitional Lewy body disease with neocortical tangles (TLBD-H). This is consistent with our recent study that relied on pathology for inclusion,[3] though the latency to diagnosis for DLBD-H in that study was longer than 2 years from cognitive onset because the time-to-event model[57] took into account those who died before meeting clinical criteria for DLB. These data provide evidence that pathologic heterogeneity and the relative distribution of $\alpha$-synuclein and tau may influence DLB phenotype and its temporal emergence. Future study is needed to understand whether differences in the timing of core features may be related to $\alpha$-synuclein strains,[58] brainstem burden,[21] patterns of spread,[59] and deposition thresholds required for clinical expression[60] across subtypes of Lewy body disease.

In the current study, inclusion required a clinical diagnosis of probable DLB. The autopsy results revealed that it is possible for probable DLB to eventually emerge in TLBD-H, despite its classification as low likelihood for probable DLB.[1] Probable DLB was also evident in a small subset of autopsy-proven AD with or without cerebrovascular disease, AD with amygdala-only Lewy bodies (AD-ALB),[32] and albeit rarely, in PSP and CJD. The basis for the DLB phenotypic expression in these groups needs to be delineated, including whether the eventual emergence of DLB core features in TLBD-H occurs when a threshold of brainstem and limbic burden of $\alpha$-synuclein pathology is reached, or by some other process.

There are several limitations to this study. It was carried out in a tertiary care setting with referral patterns that may limit generalizability to other settings. Our diagnosis of clinically probable DLB relied on the presence of clinical symptoms and did not include biomarkers.[1] Future studies that examine the onset of core features in groups classified by a single core feature and an indicative biomarker (e.g., imaging, polysomnography, cerebrospinal fluid biomarkers) or by other surrogate markers of pathology are needed. Studies that incorporate biofluid and imaging biomarkers may also help to identify Lewy body disease in patients who may be in a clinically prodromal stage of DLB, or in those with unrecognized DLB. Although informant report has the advantage of being typically used in the clinical setting and provides onset information that predates the initial visit, its use is also a major weakness given the potential for recall bias that makes it less reliable than objective or operationalized measures. In particular, the determination of fluctuations did not use a consistent operationalized approach, and may not be an accurate representation of this core feature. Studies that follow patients over time with operationalized assessment of fluctuations may provide a more reliable indication of when fluctuations developed. Larger autopsy samples are needed for further subgroup comparison, and further work is needed to

characterize the regional distribution and burden of pathology in DLB subgroups. Pathology in this study was limited by a reliance on the distribution of $\alpha$-synuclein and tau pathology, and further investigation is needed that incorporates quantitative methods of burden, regional deposition of burden, and inclusion of other pathologic features including amyloid beta, TDP-43, cerebrovascular disease, and neurotransmitter availability. Given the exploratory nature of this study, current results require verification in other cohorts.

We examined the evolution of each core feature and time to diagnosis in our large cohort of men and women with clinically probable DLB. Men and women showed some overlap in the timing of cardinal features and in the clinical expression of DLB, but also exhibited differences that warrant further investigation (Figure 3). RBD was the first core feature to emerge in both men and women, but was more common in men. Those with RBD met criteria for probable DLB at an earlier age and at a shorter latency from cognitive symptom onset than those without RBD. Women were older and had lower cognitive scores at the initial visit, were more likely to have neocortical tangles, and more likely to exhibit a delay in the time from cognitive onset to probable DLB than men. VH developed earlier in women and were more likely to emerge after the other core features in men. Understanding the phenotypic expression of DLB across the disease continuum is important for the detection of DLB, for symptom management, and for appropriate classification for the eventual implementation of protein-targeted therapies.

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## CONFLICTS OF INTEREST

PC, JAA, LF, OP, QC, TM, BD, PT, and RRR report no conflicts of interest.

## AUTHOR CONTRIBUTIONS

The following authors were involved in study conception, design, interpretation, and drafting of the manuscript: Parichita Choudhur, Tanis J. Ferman, Jonathan Graff-Radford, Bradley F. Boeve. The following authors were involved in data acquisition: Tanis J. Ferman, Bradley F. Boeve, Jonathan Graff-Radford, Ronald C. Petersen, David S. Knopman, Neill R. Graff-Radford, Toji Miyagawa, Christian Lachner, Gregory S. Day, Otto Pedraza, Hugo Botha, Rodolfo Savica, Brynn Dredla, Lincoln Wurtz, Kejal Kantarci, Julie A. Fields, Philip Tipton, R. Ross Reichard, Dennis W. Dickson. Statistical analysis was carried out by Jeremiah A. Aakre and Tanis J. Ferman. All authors were involved in manuscript revision and editing.

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