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Dementia with Lewy bodies may present as dementia and REM sleep behavior disorder without parkinsonism or hallucinations

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Abstract

Rapid eye movement (REM) sleep behavior disorder (RBD) is a sleep disturbance that commonly occurs in Dementia with Lewy bodies (DLB). Retrospective examination of DLB course has shown that RBD and cognitive decline may precede the onset of parkinsonism and visual hallucinations. Therefore, some patients with DLB may initially present with dementia and RBD, but would not meet current formal criteria for probable DLB at that time. The purpose of this study is to determine whether patients with dementia and RBD, who do not have parkinsonism or visual hallucinations, have cognitive profiles that can be distinguished from autopsy-confirmed definite AD, but not from clinically probable DLB. If so, this would support the hypothesis that the presence of RBD and dementia, as the only presenting symptoms, reflects the early manifestation of DLB. Results show that early dementia in probable DLB and dementia with RBD are neuropsychologically indistinguishable. Both groups differ from definite AD of a similar early stage with significantly worse visual perceptual organization, sequencing and letter fluency but significantly better confrontation naming and verbal memory. In addition, follow-up data from a subset of patients with dementia and RBD reveal the subsequent development of parkinsonism or hallucinations 1 to 6 years later. Results indicate that the presentation of dementia and RBD is suggestive of underlying Lewy body disease and not Alzheimer's disease. This provides further evidence in support of including RBD as one of the core diagnostic features of DLB. (*JINS*, 2002, *8*, 907–914.)

Keywords: REM sleep behavior disorder, Dementia with Lewy bodies, Parkinsonism, Visual hallucinations, Lewy body disease, Alzheimer's disease

INTRODUCTION

Rapid eye movement (REM) sleep behavior disorder (RBD) occurs in human neurodegenerative diseases known to affect the brainstem, including Parkinson's disease (PD) (Schenck et al., 1996), dementia with Lewy bodies (DLB) (Boeve et al., 1998; Turner et al., 1997) and multiple system atrophy (Plazzi et al., 1997). In contrast, RBD is rarely reported in the cortical neurodegenerative conditions of Alzheimer's disease (AD) or frontotemporal dementia (Boeve et al., 2001a). Therefore, a determination of RBD may be particularly helpful in the differential diagnosis of some types of dementia. RBD involves a loss of normal paralysis during REM sleep resulting in the emergence of coordinated movements that appear to mirror dream activity. In patients with RBD, overnight polysomnogram monitoring reveals augmentation of electromyographic (EMG) tone during REM sleep, indicating REM sleep without atonia. In

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the cat model, REM sleep without atonia is attributable to the focal disruption of specific brainstem circuits, and the degree of motor complexity exhibited during REM sleep is associated with lesion size (Hendricks et al., 1982; Schenkel & Siegel, 1989).

Parkinsonism, visual hallucinations and fluctuating cognition are considered core clinical features of DLB. Dementia plus one core feature is required for a diagnosis of possible DLB, and at least two core features are needed for a diagnosis of clinically probable DLB (McKeith et al., 1996). Although not currently recognized as a core diagnostic criterion, the presence of RBD in patients with dementia has been associated with DLB (Boeve et al., 1998; Turner et al., 1997) and is considered a supportive feature of the DLB diagnosis (McKeith et al., 1999). Clinical evidence of this relationship was found in a prior study of 31 patients with dementia and a history of RBD, in that the criteria for possible or probable DLB was met in all but 1 patient (Ferman et al., 1999). In addition, the cognitive profile differed from that of patients with pathologically confirmed definite AD. When histopathologic data from 11 patients with RBD and neurodegenerative disease were examined, 10 had neuropathologic diagnoses of Lewy body disease (PD or DLB) and 1 patient had multiple system atrophy (Boeve et al., 2001b). Turner et al. (2000) identify a patient with a clinical diagnosis of DLB plus a 17 year history of polysomnogram-confirmed RBD in whom Lewy body pathology was found on autopsy. Uchiyama et al. (1995) describe a patient with idiopathic RBD of 20 years duration with no parkinsonism, dementia or psychiatric symptoms but neuropathologic findings revealed Lewy bodies in the brainstem and limbic regions. These studies provide convincing clinical and neuropathologic evidence that RBD is associated with Lewy body disease.

Is it possible that patients with DLB may initially present with dementia and RBD in the absence of other core features of DLB? When the course of DLB is retrospectively examined, the estimated onset of RBD typically precedes the onset of the dementia, visual hallucinations and parkinsonism by many years. Specifically, RBD has been shown to herald the onset of neurodegenerative symptoms over a broad time range, including an average of 7.5 years prior to the development of DLB in one study (Boeve et al., 1998) and an average of 12.7 years prior to the development of parkinsonism in another study (Schenck et al., 1996). Cognitive impairment in patients with DLB has been shown to precede the development of visual hallucinations and parkinsonism, by about 1 year (Ferman et al., 1999; Turner et al., 1997). The onset of dementia in relation to the feature of fluctuating cognition in DLB, however, has not been established and may be potentially difficult to disentangle since both have cognitive dysfunction as a defining component. Nonetheless, the possibility that dementia and RBD may precede the onset of two of the three core features of DLB has implications for early diagnosis. It raises the possibility that some patients with DLB may initially present with dementia and RBD, but until parkinsonism or visual hallucinations become apparent, a diagnosis of probable DLB would not be made. The purpose of this study is to determine whether patients with RBD and dementia, who do not have parkinsonism or hallucinations, have a dementia that neuropsychologically resembles probable DLB and differs from AD. If so, this would provide evidence that DLB may initially manifest itself as dementia with RBD.

METHODS

Patients and Procedures

This study included three groups: (1) 37 patients (31 M, 6 F) with clinically probable DLB; (2) 25 patients (24 M, 1 F) with dementia plus RBD who do not have a history of visual hallucinations or parkinsonism; and (3) 30 patients (10 M, 21 F) with pathologically confirmed definite AD. The probable DLB and dementia with RBD groups comprise a retrospective sample initially referred to the Mayo Department of Neurology or to the Mayo Sleep Disorders Center from 1993 through 2000. The autopsy confirmed AD group consisted of consecutive patients prospectively followed through the Mayo Alzheimer's Disease Research Center from 1989 through 1998.

Inclusion criteria for all groups required documentation of an insidious and progressive cognitive decline that significantly interfered with complex activities of daily living. In addition, the Global Deterioration Scale (GLDS), a measure of functional decline and stage of dementia, was used to determine the level of dementia severity, independent of neuropsychological assessment (Reisberg et al., 1988). Patients with GLDS scores of 2 or less were excluded because this is not considered to be within the range of dementia. Application of the GLDS to the dementia with RBD group revealed scores of 3 or 4 only, representing mild or mild to moderate levels of functional impairment. In an effort to match patient groups on overall stage of dementia severity, only those patients in the DLB and AD groups with GLDS scores of 3 or 4 were included. Therefore, this study involves a comparison between patients at a relatively early stage of dementia.

The AD group was selected on the basis of meeting clinical and neuropathologic CERAD criteria for definite Alzheimer's disease with no histopathologic evidence of brainstem Lewy bodies. Patients with AD were excluded if they had auditory or visual hallucinations before or at the time of neurocognitive examination based on Part C of the Record of Independent Living (Weintraub, 1986), the Behavior Problem Checklist (Stotsky, 1990) or the Neuropsychiatric Inventory (Cummings, 1997). A subset of patients in the current study (i.e., 13 DLB, 8 dementia with RBD and 22 AD) were also included in a previously published study (Ferman et al., 1999).

All patients in the DLB group fulfilled formal criteria for probable DLB (McKeith et al., 1996), which requires the presence of dementia plus two or more of the following clinical features: (1) parkinsonism, (2) visual hallucina-

tions, and (3) fluctuating cognition/alertness. Patients with a history of clinical or imaging evidence for stroke or relevant cerebrovascular disease were excluded from the study.

Clinical information for the probable DLB and dementia with RBD groups were obtained from retrospective chart review of outpatient clinic visits. Core features of DLB were considered present if documented at the time of the neurocognitive evaluation. All patients underwent a clinical neurologic examination and the presence or absence of extrapyramidal signs was abstracted from the chart. Specifically, parkinsonism was considered present if two or more of the cardinal signs (rigidity, bradykinesia, postural instability, resting tremor) were reported. Since data was obtained from the clinical records, no standardized scales designed to assess parkinsonism were used (e.g., Unified Parkinson's disease rating scale). Presence or absence of hallucinations was consistently documented as part of the sleep, neurologic and/or neuropsychologic evaluations for each patient. Patients were considered to have visual hallucinations if the patient had recurrent, fully formed visual images of people, animals or objects that others did not see. The presence of extrapyramidal signs and visual hallucinations before or at the time of testing excluded patients from the dementia with RBD group. Fluctuating cognition was counted if there was documentation of recurrent alternating episodic daytime confusion with periods of lucidity, times when the patient was unable to carry out certain tasks that he or she could normally or nearly normally perform later, periods of unresponsiveness while awake (i.e., blanking out, zoning out) or fluctuating arousal during the daytime despite adequate nighttime sleep. Eight patients from the dementia with RBD group, and 7 patients from the DLB group did not have documentation indicating either the presence or the absence of the above aspects of fluctuating cognition. Since little is known about fluctuating cognition, it was recorded when thought to be present based on the criteria listed above, but the presence of this feature did not serve to exclude patients from the dementia with RBD group. Information regarding the presence of fluctuating cognition in the AD group was not available.

A history of RBD was required for inclusion in the dementia with RBD group, and was documented as present or absent in the probable DLB group. Patients were diagnosed with RBD when minimal diagnostic criteria for RBD was fulfilled (American Sleep Disorders Association, 1997). This includes a complaint of violent or injurious behavior during sleep, limb or body movement associated with dream mentation *and* at least one of the following: (1) harmful or potentially harmful sleep behaviors, (2) dreams that appear to be "acted out," (3) sleep behaviors that disrupt sleep continuity. If polysomnographic monitoring was obtained, then excessive augmentation of electromyographic (EMG) tone during REM sleep or excessive chin or limb phasic EMG plus excessive limb jerking or complex behaviors during REM sleep was required. Overnight polysomnography was available for 59% and 60% of the probable DLB and dementia with RBD groups, respectively.

In this study, neuropsychological tests given commonly between groups were used in the statistical comparisons. In some patients, multiple assessments were performed longitudinally, and in such cases, only the first assessment was included in this analysis. The Mattis Dementia Rating Scale (Mattis, 1988) was obtained for the purpose of obtaining a cognitive measure of global dementia severity. Age-corrected scaled scores ($M = 10$, $SD = 3$) were obtained from the Mayo Older American Normative Studies (MOANS) for subtests of the Wechsler Adult Intelligence Scale–Revised (WAIS–R; Ivnik et al., 1992a), Boston Naming Test (BNT; Ivnik et al., 1996), Controlled Oral Word Association Test (COWAT; Ivnik et al., 1996), and subtests of the Wechsler Memory Scale–Revised (WMS–R; Ivnik et al., 1992b).

RESULTS

Clinical Data

GLDS scores of functional impairment indicated mild and mild to moderate levels of dementia severity, based on selection criteria. Performance on the Mattis Dementia Rating Scale substantiates that degree of dementia does not differ between groups, and also places global dementia severity at a relatively early stage (see Table 1). Education did not differ between groups, but the AD group was significantly older than the other two groups [$F(2,91) = 23.8$, $p < .01$]. Given the age difference between patients with AD and the other two groups, age-adjusted scaled scores were used in the comparisons of neurocognitive performance. Chi-square analysis showed that more men than women were represented in the probable DLB and dementia with RBD groups than in the AD group [$\chi^2(2,92) = 31.9$, $p < .05$].

In the probable DLB group, 22 patients exhibited two or more extrapyramidal signs, 23 had fully formed recurrent visual hallucinations, 34 were considered to have fluctuating cognition, and 33 had a history of RBD. In the dementia with RBD group, 15 patients were considered to have fluctuating cognition.

The average duration of RBD was 9 years (see Table 1) with a range of 6 months to 52 years. Duration of RBD did not significantly differ between DLB and dementia with RBD groups. Overnight polysomnography was obtained in 22/37 individuals from the probable DLB group and in 15/25 individuals from the dementia with RBD group. The polysomnogram data revealed REM sleep without atonia, which is the electrophysiologic substrate of RBD, in all but four patients. For 3 of these 4 patients, there was a complete absence of REM sleep and one patient demonstrated a non-REM sleep parasomnia. When patients with a history of RBD were compared on the basis of polysomnogram confirmation of REM sleep without atonia, there was no statistically significant difference in duration of RBD [$F(1,35) = 0.63$, $p > .05$], age [$F(1,36) = 0.01$, $p > .05$], education [$F(1,36) = 0.45$, $p > .05$] or duration of cognitive decline [$F(1,36) = 0.36$, $p > .05$].

Table 1. Age, education, duration of cognitive decline, RBD and Dementia Rating Scale score

	Probable DLB		Dementia with RBD		Definite AD			
Parameter	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*
Age, years	71.0[a]	7.3	69.5[a]	8.1	81.5[b]	6.6	23.8	.00*
Education, years	13.5	3.5	14.6	2.9	13.1	3.0	1.47	.24
Duration of decline, years	2.7	2.0	2.4	1.6	2.8	2.2	0.32	.72
RBD age of onset, years	60.5	14.1	61.8	13.1	—	—	0.12	.73
Duration of RBD, years	10.2	13.3	7.5	12.2	—	—	0.60	.44
DRS total score	117.5	11.8	117.0	10.0	116.7	10.5	0.22	.80

*$p < .01$.
[a,b]Least squares difference *post-hoc* tests, $p < .05$. Groups with the same letter indicate no significant difference while groups with different letters indicate significant difference.
Duration of decline = cognitive decline; RBD = REM Sleep Behavior Disorder; DRS = Mattis Dementia Rating Scale.

Neurocognitive Data

One-way analyses of variance were used to examine group differences on neurocognitive measures and pairwise multiple comparisons *post-hoc* analyses were carried out when significant main effects were obtained (see Table 2). There were no statistically significant differences between the probable DLB and dementia with RBD groups across cognitive domains measured, despite adequate power to detect group differences. The probable DLB and dementia with RBD groups demonstrated moderate impairment on a perceptual organization task (Block Design) in comparison to mildly impaired performance on this task for the AD group [$F(2,81) = 21.24$, $p < .01$]. Block Design performance in the DLB and RBD groups revealed problems with visual perception and organization, and did not appear to be due to motor slowness. The probable DLB and dementia with RBD groups also showed significantly worse performance than the AD group on a visual sequencing task of pictured situations [Picture Arrangement: $F(2,71) = 7.65$, $p < .01$] and speeded generation of words beginning with particular letters [Controlled Oral Word Association Test: $F(2,85) = 7.35$, $p < .01$].

In contrast, delayed verbal memory for paragraph material was moderately impaired for the AD group but only

Table 2. Neurocognitive performance across patient groups (age adjusted scaled scores)

	Probable DLB			Dementia with RBD			Definite AD				
Parameter	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*F*	*p*
WAIS–R											
Information	31	8.26	3.88	19	8.63	2.19	30	6.83	2.62	2.48	.09
Vocabulary	31	7.74	3.00	19	9.00	2.44	29	7.83	2.82	1.36	.26
Digit Span	31	8.06	2.96	21	7.95	2.97	29	8.10	3.19	0.16	.98
Arithmetic	32	6.34	2.54	20	6.95	2.39	28	7.00	2.89	0.56	.57
Picture Completion	31	5.58[a]	2.49	17	7.05	2.79	28	8.18[b]	2.46	7.70	.00*
Picture Arrangement	30	6.53[a]	2.30	17	7.41[a]	2.03	25	8.84[b]	2.13	7.65	.00*
Block Design	32	3.13[a]	1.86	21	3.19[a]	2.18	29	6.86[b]	3.15	21.24	.00*
WMS–R											
Logical Memory I	35	4.97	2.54	24	6.04	2.82	24	4.58	2.10	2.21	.12
Logical Memory II	35	5.57[a]	2.87	24	6.38[a]	3.04	24	3.71[b]	2.00	6.10	.01*
Logical Memory % ret	35	7.60[a]	4.24	24	7.83[a]	3.82	24	4.69[b]	4.24	4.39	.02**
Visual Reproduction I	35	3.54	2.12	24	4.67	2.60	24	4.38	2.46	1.80	.17
Visual Reproduction II	35	4.09	2.10	24	5.00	2.48	24	4.50	2.02	1.13	.32
Visual Reproduction %ret	35	5.94	3.22	24	6.34	3.56	24	5.50	3.34	0.30	.74
COWAT	36	5.83[a]	2.26	21	6.71[a]	3.19	29	8.28[b]	2.40	7.35	.00*
BNT	34	7.97[a]	3.42	17	8.00[a]	3.33	27	5.93[b]	3.14	3.40	.04**

Age-corrected scale scores ($M = 10 \pm 3$) for Wechsler Adult Intelligence Scale–Revised (WAIS–R), Wechsler Memory Scale–Revised (WMS–R), Boston Naming Test (BNT), and Controlled Oral Word Association Test (COWAT).
*$p \leq .01$, **$p < .05$.
[a,b] = groups with the same letter indicate no significant difference while groups with different letters indicate significant difference based on least squares difference *post-hoc* tests $p < .05$.

mildly impaired for the probable DLB and dementia with RBD groups [$F(2,82) = 6.10$, $p < .01$]. Percent retention of the paragraph material was 21% for the AD group, which significantly differed from 53% for the DLB group and 58% for the dementia with RBD group [$F(2,81) = 9.08$, $p < .01$]. The AD group also had significantly greater difficulty with confrontation naming relative to the performance exhibited by the other two groups [$F(2,77) = 3.40$, $p < .05$].

The probable DLB group demonstrated worse performance at identifying missing visual features in line drawings (Picture Completion) than AD patients [$F(2,75) = 7.70$, $p < .01$], while performance for the dementia with RBD group yielded no statistically significant difference from either the probable DLB or AD groups. Performance on tasks of visual memory, general vocabulary, access to remote knowledge, immediate attention span and arithmetic did not statistically differ between groups. Comparisons between patients with and without polysomnogram verification of REM sleep without atonia showed no significant differences in cognitive performance.

Clinical Follow-Up

Clinical follow-up data based on chart review of return visits a year or more after the neurocognitive evaluation was available for 14 patients in the dementia with RBD group. Of these, 2 died of unknown causes a year after their evaluation, 3 had not developed parkinsonism or visual hallucinations by 1-year follow-up, and 9 developed one or both features. Specifically, 2 patients developed visual hallucinations by their 1- and 3-year follow-up evaluations, which was 3 and 4 years following the estimated onset of cognitive decline, respectively. Seven patients developed parkinsonism by their follow-up evaluations, with 3 patients having developed it within 1 year after initial evaluation, 3 having developed it by their 3-year follow-up, and 1 patient who developed it 6 years later. The extrapyramidal symptoms for these patients developed from 3 to 7 years following the estimated onset of cognitive decline.

Autopsy data were available for 2 patients from the DLB group. Both patients had widespread cortical and subcortical Lewy body pathology and few neocortical neuritic plaques. Both patients had sparse neurofibrillary tangles with a Braak stage III for 1 patient, and a Braak stage IV for the other patient.

DISCUSSION

Despite the absence of visual hallucinations and parkinsonism, dementia with RBD is neuropsychologically indistinguishable from that of clinically probable DLB at a similar early stage of dementia. Moreover, cognitive performance of patients with probable DLB and dementia with RBD significantly differs from that of patients with autopsy-confirmed definite AD of similar dementia severity. Visual perceptual organization, sequencing skills and letter fluency are significantly worse in probable DLB and dementia with RBD than in AD. In contrast, verbal memory and confrontation naming are significantly worse in AD than in probable DLB or dementia with RBD. These data support the hypothesis that the dementia associated with RBD is likely to be DLB, even in the absence of parkinsonism and visual hallucinations.

Visual perceptual organization and visual sequencing difficulties represent the most striking aspect of the cognitive presentation of early DLB and dementia with RBD. Current findings are consistent with prior reports of disproportionately poor performance on visual tasks for DLB relative to AD, a finding that is not attributable to motor slowness (Boeve et al., 1998; Ferman et al., 1999; Hansen et al., 1990; Salmon et al., 1996). Nonetheless, naming and identification of familiar objects is relatively preserved in the early stages of DLB, suggesting that contextual cues may help with visual discrimination. What is the proposed mechanism underlying the visual processing deficits in DLB and dementia with RBD? Through a series of experimental visual tasks of varying complexity, the visual processing difficulties in DLB have been attributed to deficits in elementary visual perceptual processing (Mori et al., 2000). Regional cerebral blood flow has been shown to be lower in the occipital regions for DLB relative to AD (Ishii et al., 1999; Lobotesis et al., 2001). Lewy bodies are thought to rarely affect the primal visual cortex, but there is speculation that depletion of cholinergic or dopaminergic systems in DLB may affect the pathways subserving the visual system (Lobotesis et al., 2001). Lewy bodies and spongiform changes have been found in the temporal lobe (Byrne et al., 1989; Dickson et al., 1987), but whether this extends to occipito–temporal regions associated with visual perception (Ungerleider & Haxby, 1994) has not yet been determined.

Memory difficulties, when present in early DLB and in dementia with RBD appear to be fairly mild. Formal testing reveals that patients with probable DLB and dementia with RBD demonstrate better learning and memory for logically organized verbal material than patients with AD, but there are no group differences when the to-be-learned material involves constructing visual figures. Generalized learning and memory deficits may account for AD performance, while visual processing difficulties (Mori et al., 2000) and constructional dyspraxia (Boeve et al., 1998) may explain the selective impairment of visual memory in the probable DLB and dementia with RBD groups. If so, than this would suggest greater mesial temporal involvement in AD than for DLB. Indeed, imaging studies reveal greater hippocampal atrophy in AD than DLB (Barber et al., 1999; Hashimoto et al., 1998) and preserved regional cerebral blood flow of mesial temporal regions in DLB compared to AD (Ishii et al., 1999; Lobotesis et al., 2001). There are also differences in the regional distribution of hippocampal pathology between these disorders. In AD, neuronal loss and histopathology are typically found in hippocampal area CA1 (Arnold et al., 1991), while in DLB, this region of the hippocampus is typically spared of neuro-

pathology (Dickson et al., 1994). Moreover, when hippocampal Lewy bodies and Lewy neurites are present, they are typically found in the CA2/3 region, a region that is largely spared in AD (Dickson et al., 1991; 1994). This suggests that the pattern of memory performance may also differ between DLB and AD. In one study of list learning, Salmon et al. (1996) found that of 5 patients with DLB, four showed a pattern of poor initial learning and retrieval, but not the rapid rate of forgetting typically associated with mesial temporal dysfunction. Current findings also reveal greater deficits in percent retention of verbal material for the AD group than for the DLB and Dementia with RBD groups, providing evidence of rapid forgetting in AD but not the other two groups. There is also a subtle, but apparent, dissociation of confrontation naming and letter fluency performance between early AD and the clinical groups of DLB and dementia with RBD. Naming and memory deficits are typically early features of AD (Jacobs et al., 1995a), while slowed verbal fluency is an early component of the so-called subcortical dementia syndromes (Jacobs et al., 1995b).

Autopsy data available for two patients from the DLB group demonstrated widespread and frequent cortical and subcortical Lewy body pathology, sparse neuritic plaques and sparse neurofibrillary tangles. This is consistent with reported neuropathologic findings associated with DLB in which the Lewy body pathology predominates, but Alzheimer pathology may also be present. When AD pathology is found, neuritic plaque density is the same or much less in DLB than in AD, while neurofibrillary tangle density has been shown to be significantly less frequent in DLB than in AD (Gomez-Tortosa et al., 1999; Hansen et al., 1990, 1993; Lippa et al., 1994). In AD, the severity of cognitive impairment is associated with neurofibrillary tangle density and not plaque density (Arriagada et al., 1992). In DLB, dementia severity is not associated with neurofibrillary tangle count (Samuel et al., 1996; 1997) but is related to Lewy body density even after the contribution of neuritic plaques and neurofibrillary tangles are taken into account (Haroutunian et al., 2000; Mattila et al., 2000).

Although follow-up data for patients with dementia and RBD is limited, 9 of these patients did develop visual hallucinations and/or parkinsonism from 1 to 6 years after the initial evaluation, and 3 to 7 years after the estimated onset of cognitive decline. These results indicate that patients who initially present with dementia and RBD can go on to develop other features of DLB.

This study contains the limitations inherent to retrospective designs, including a less expansive selection of tests and presence of missing data due to test battery differences. The AD group was significantly older than the other two diagnostic groups; however, use of age-adjusted standardized scores and normative reference data corrected for this potential limitation. In addition, men predominantly comprised the DLB and dementia with RBD groups, but this is a pattern that has also been observed in other studies of DLB (Klatka et al., 1996). A potential criticism is that RBD may be mistaken for obstructive sleep apnea, non-REM sleep parasomnias (e.g., somnambulism, confusional arousals) or nocturnal seizures, and as such, obtaining overnight polysomnography is important for differential diagnosis of the underlying sleep disturbance. We agree that obtaining an overnight polysomnogram is critical for verifying the diagnosis of RBD. Polysomnography was obtained in over half the patients with DLB and dementia with RBD in this study, and this revealed confirmation of REM sleep without atonia in all but 3 patients. Of these remaining 3, 2 did not exhibit REM sleep at all (and as such, REM sleep atonia was not measurable) and 1 had a non-REM sleep parasomnia. These data suggest that our use of the clinical diagnostic criteria of RBD in the remaining sample is likely to be reasonably accurate.

A proportion of patients in the dementia with RBD group have symptoms of fluctuating cognition and alertness and therefore, some patients in this group technically meet criteria for possible DLB. This is a weakness of the study, but there is currently no clearly defined operational definition of fluctuating cognition and the reliance on retrospective chart review has inherent limits regarding whether or how this feature was recorded. Further work is needed to determine the essential features of fluctuating cognition found in DLB (and dementia with RBD) that may be differentiated from potential day to day variations found in AD. At this stage of our understanding of fluctuating cognition, rarely would the diagnosis of DLB be made on the basis of dementia and fluctuating cognition alone. Nonetheless, current data indicate that obtaining a clear history of RBD and dementia, with or without fluctuating cognition, should raise suspicion for a diagnosis of DLB.

The association between RBD and neurodegenerative disorders points to involvement of the brainstem, and seems most prevalent in disorders that involve an abnormal accumulation of the intracellular protein alpha-synuclein (i.e., PD, DLB, and multiple system atrophy; Boeve et al., 2001a; Dickson et al., 1999; Plazzi et al., 1997; Schenck et al., 1996). In the cat, REM sleep generation and normal REM sleep atonia have been associated with function of the cholinergic and glutamatergic cells in the pedunculopontine nucleus (Garcia-Rill, 1991; Shouse & Siegel, 1992) and in the pontomedullary descending reticular formation, respectively (Hendricks et al., 1982; Lai et al., 1999). These regions in the brainstem are in close proximity to areas known to be associated with motor control and arousal. The early presentation of RBD relative to other symptoms of DLB may reflect differences in the critical threshold of cell loss or neurotransmitter depletion in the neuronal pathways needed for the emergence of specific symptoms. For example, the symptoms of parkinsonism and RBD may occur through disruption of nearby interconnected, but distinct, neuronal pathways subserving extrapyramidal motor function and normal REM sleep atonia.

Results of this study indicate that a clinical history of RBD in the context of a dementia with disproportionate visual deficits is likely to represent the earliest stages of

DLB. This adds to the already well established finding that RBD heralds the onset of Lewy body disease (Boeve et al., 1998, 2001a; Ferman et al., 1999; Schenck et al., 1996; Turner et al., 1997). It also provides further support for the inclusion of RBD as a core clinical feature in the diagnostic criteria for DLB.

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