Longitudinal Study of Cognitive Function in Idiopathic REM Sleep Behavior Disorder

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Study Objectives: To assess the longitudinal course of cognitive functions in a cohort of patients with idiopathic REM sleep behavior disorder (iRBD).

Design: Prospective study with baseline and 2-year follow-up.

Setting: Sleep disorders center.

Participants: Twenty-four cognitively asymptomatic iRBD patients (18 M; mean age: 69.5 ± 7.3 y) and 12 sex-, age-, and education-matched healthy subjects.

Interventions: Participants underwent to a video-PSG, a focused neuropsychological evaluation and a neurological examination. Following the first evaluation, subjects were reassessed after a mean interval of 25.8 months.

Measurements and Results: Executive functions, attention and language were normal at baseline and at 2 year follow-up examination. At baseline, iRBD patients showed poorer performance than controls in delayed verbal memory (story recall test: P = 0.001) and in visuo-constructional abilities (Copy of the Rey-Osterrieth complex figure: P = 0.0005). At follow-up, they not only performed worse than controls in the same tests (story recall: P = 0.0001; Copy of the Rey-Osterrieth complex figure: P = 0.0004), but they also showed an impairment in visuo-spatial learning (Corsi supraspan test; P < 0.0001). ANOVAs showed a significant worsening in visuo-spatial learning over time in RBD compared to controls (P = 0.0001). Furthermore, 3 patients fulfilled the UK Brain Bank criteria for Parkinson disease, but this was unrelated to cognitive deterioration.

Conclusions: Although no patients developed dementia, the decline observed in some tests involving the memory and visuo-constructional domains in idiopathic RBD suggests the presence of an underlying evolving degenerative process.

Keywords: REM sleep behavior disorder, neuropsychological functions, neurodegenerative diseases

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INTRODUCTION

REM sleep behavior disorder is a parasomnia characterized by complex motor activity emerging from REM sleep and usually associated to action-filled dream mentation.[1-3] Clinical follow-up studies show that a remarkable proportion of patients affected by RBD develop a neurodegenerative disorder, mostly of α-synucleinopathy type,[4-6] and that this proportion increases significantly with time.[7-9] Possible early signs of neurodegeneration, such as EEG slowing, subtle neuropsychological deficits, mild parkinsonism, olfaction dysfunction, color vision impairment, and reduced cardiac sympathetic innervation were found in patients with idiopathic RBD,[10] although the predictive value of each single alterations for the evolution toward a neurodegenerative disease remains unclear. Recently, combined striatal dopamine transporter uptake and substantia nigra hyperechogenicity were found to be predictive of conversion to a synucleinopathy.[11]

A variety of neuropsychological deficits have been observed in idiopathic RBD patients, involving visuospatial functions (e.g., visuo-constructive abilities and visuo-spatial learning),[12] executive functions, and verbal memory,[13,14] often fulfilling standard criteria for mild cognitive impairment (MCI).[15,16]

Results of these studies are not always univocal in identifying the main area of impairment in idiopathic RBD. Differences in sociodemographic characteristics of patients and control subjects and in test sensitivity, as well as small sample sizes, have been invoked to explain such discrepancies. Nevertheless, the cognitive profile of idiopathic RBD emerging from all these studies, including both visuospatial and executive dysfunctions, appears to be similar to that observed in *α*-synucleinopathies, particularly in Lewy body disease. Indeed visuo-perceptual dysfunctions represent a distinctive feature of dementia with Lewy body (DLB), since its early stage, when compared with Alzheimer disease (AD).[17,18] Furthermore, when RBD is associated with a degenerative dementia, the latter has the clinical and pathological features of DLB,[6,19,20] and RBD represents a suggestive feature for the diagnosis of DLB.[21] On the other hand, as pointed out by Molano et al.,[16] the MCI picture associated with idiopathic RBD is of the non-amnestic single or multiple domain type, with an eventual postmortem-confirmed Lewy body disease. Thus, it has been postulated that cognitively impaired idiopathic RBD patients might be more at risk of developing a neurodegenerative dementia than those with normal cognitive function. It remains to be ascertained whether neuropsychological impairment is an early marker of an ongoing neurodegenerative process, or simply represents a non-evolving associated feature of the parasomnia. Indeed, so far no study has assessed the long-term evolution of the neuropsychological deficits

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Table 1—Neuropsychological tests administered and explored functions

Neuropsychological Test	Explored Function
MMSE§	Screening for dementia
Memory	
Digit span forward§	Short-term verbal memory
Digit span backward§	Working memory
Corsi block tapping task§	Short-term spatial memory
Corsi supraspan	Visuo-spatial learning
Story recall	Delayed verbal memory
Rey-Osterrieth complex figure delayed recall	Delayed visuo-spatial memory
Executive functions	
Raven's progressive matrices	Nonverbal reasoning
Attentional matrices	Visual selective attention
Stroop color word interference test§	Inhibition and selective attention
Trail Making Test (A)§	Cognitive set shifting
Trail Making Test (B)	Cognitive set shifting
Trail Making Test (B/A)	Cognitive set shifting
Phonemic fluency	Verbal production ability
Semantic fluency	Verbal production ability
Visuo-spatial abilities	
Rey-Osterrieth complex figure copy§	Visuo-constructional abilities

§Non parametric test (Mann-Whitney U).

found in idiopathic RBD. The aim of the present study was to assess the longitudinal course of neuropsychological functions in a cohort of idiopathic RBD compared to age and gender-matched healthy subjects.

METHODS

Subjects

Twenty-four patients diagnosed with idiopathic RBD (18 M, 6 F; mean age: 69.5 ± 7.3; age range: 55-83 y, average education: 8.6 ± 3.6 y) and 12 healthy subjects matched for age, gender, and education (9M, 3F; mean age: 69.3 ± 6.3 y; age range: 53-82 y; average education: 8.3 ± 4.0 y) were enrolled in the study. RBD patients fulfilled the standard criteria for RBD[22] namely the presence of excessive phasic or tonic electromyographic (EMG) activity during REM sleep, associated to either history of disruptive and injurious sleep behavior, or videopolysomnography (vPSG)-confirmed abnormal behaviors during REM sleep. Control subjects were recruited among outpatients of a general practitioner clinic. None had history of head trauma, cerebrovascular disease, neurological conditions, or sleep disorders such as parasomnia or obstructive sleep apnea syndrome.

None of the patients or the controls complained of cognitive decline. Dementia and depression were ruled out according to Diagnostic and Statistical Manual of Mental Disorders IV criteria.[23] Subjects with an age- and education-corrected score < 24 on the Italian version of the Folstein Mini Mental State Examination (MMSE)[24] and with a score > 20 on the Beck Depression Inventory[24] were excluded. Subjects underwent a standard neurological examination, including the motor scale of the Unified Parkinson Disease Rating Scale (UPDRS)-III.[26] The latter was used as a checklist to assess signs of parkinsonism. Five patients were taking clonazepam at the initial time of the study (mean dose: 0.59 ± 0.28 mg), and one patient was taking melatonin at the dose of 3 mg in addition to clonazepam. The study was approved by the local ethical board and subjects gave written consent.

Procedures

PSG recording

Patients and controls underwent one-night of video-polysomnographic (v-PSG) recording at the time of first evaluation, to either confirm or rule out the diagnosis of RBD. Sleep was recorded and scored according to Rechtschaffen and Kales' method, using 30-sec epochs. PSG included electroencephalographic recording (C3/A2, C4/A1, according to the 10-20 international electrode placement system), right and left electrooculogram, and chin electromyogram. Recording of oral and nasal air-flow, thoracic and abdominal movements, and oximetry was performed to detect apneas or hypopneas. Surface EMG of the right and left anterior tibialis muscles was recorded to quantify leg movements. Electrocardiogram was recorded from a standard D2 lead. Periodic leg movements during sleep (PLMS) were recorded and scored according to ICSD-2 criteria,[22] i.e., leg movements lasting 0.5-5 sec, separated by intervals of 5-90 sec, and occurring in series of ≥ 4 consecutive movements. Microarousals were scored on the C3-A2 EEG lead using the ASDA criteria,[27] and microarousal index (number per hour of sleep) was calculated.

Neuropsychological evaluation

Subjects underwent a focused neuropsychological examination, assessing the cognitive domains (memory, executive function, and visuo-spatial processing) frequently affected in RBD (see Table 1). The test battery, which required approximately 1.5 h to complete, included the MMSE.[24] The memory assessment included tests of short-term verbal and spatial memory (digit span forward and Corsi block-tapping test)[28,29]; a working memory test (digit span backward)[30]; a test of long-term verbal memory (story recall), requiring the immediate and delayed (after 10 min) recall of a short story[31]; spatial learning (Corsi supraspan learning test)[32]; and delayed spatial memory (delayed recall of the Rey-Osterrieth complex figure).[33]

The executive functions assessment included nonverbal reasoning (Raven's Progressive Matrices)[29]; inhibition and selective attention (Stroop color word interference test); cognitive set shifting (Trail Making Test A and B)[34]; visual selective attention (attentive matrices)[34]; and verbal fluency with phonemic and semantic cues.[29] Visuoconstructional abilities were assessed with the copy of Rey-Osterrieth complex figure.[33] The tests were administered and scored according to published procedures.[35] The raw scores were converted in Equivalent Scores, calculated on the ranks of the original scores adjusted for age, education (and for the influence of the patient's sex when appropriate): 0 corresponds to a score lower than the inferential 5th centile of the normal popula-

Table 2—Clinical and demographic characteristics of RBD patients and controls

	Idiopathic RBD (n = 24)	Controls (n = 12)	P
Age (y)	69.5 ± 7.3	69.3 ± 6.3	NS
Gender	18M; 6F	9M; 3F	NS
Mean duration of RBD	7.6 ± 7.3	-	-
Mean UPDRS-III score	4.2 ± 3.7	2.2 ± 1.7	NS
Education (y)	8.6 ± 3.6	8.3 ± 4.0	NS
Mean duration of follow up (months)	26.3 ± 5.0	25.5 ± 2.0	NS
BDI score	8.2 ± 5.2	5.3 ± 4.4	NS

tion with 95% confidence; 4 corresponds to a score higher than the median value of the normal population, and 1, 2, and 3 are intermediate points between 0 and 4 on a quasi-interval scale.

Following the first evaluation, patients and control subjects were reassessed by means of the same test battery after a time interval of approximately 2 years. Tests were administered by the same investigator (EF). Scoring of several tests, namely both the copy and the delayed recall of the Rey-Osterrieth complex figure, and the Story recall test were scored by an expert neuropsychologist (PO), blinded to the diagnosis.

Clinical relevance of cognitive impairment

For each test, equivalent scores were calculated,[32] and the number of subjects with abnormal score in each group was assessed. Both 1 (borderline) or 0 (pathological) scores were considered abnormal.

Statistical Analysis

Data were assessed for normality (Shapiro-Wilk test), and Student *t*-tests were performed to assess between-group differences on demographical, clinical, PSG, and neuropsychological variables that were normally distributed. Mann-Whitney U test was performed to assess between-group differences in variables that were not normally distributed. Bonferroni correction was applied to reduce the possibility of type II error, and level of significance was set accordingly. Changes in cognitive performances over time in the two groups were assessed by 2-way analysis of variance (ANOVAs) for repeated measures with Group as independent factor and Time as within-subjects factor. Before statistical analysis, a log transformation was performed on values of neuropsychological tests to normalize data distribution. Correlations between neuropsychological measures and clinical and demographical variables were assessed by Pearson product-moment correlations. The difference in distribution of abnormal scores between patients and controls was assessed by means of Fisher exact test.

RESULTS

Demographical and clinical data of RBD patients and controls are shown in Table 2. There were no differences in age, education, mean UPDRS-III score, and mean BDI score at baseline. PSG characteristics of RBD patients and control subjects at baseline are shown in Table 3. The 2 groups did not differ in terms of sleep architecture or microarousal index, but PLMS index was significantly higher in RBD patients than control subjects.

The results of neuropsychological tests at baseline are reported in Table 4. Patients with RBD showed poorer perfor-

Table 3—Polysomnographic characteristics of patients with RBD and control subjects

	RBD patients n = 24	Control subjects n = 12	P
Sleep latency (min)	24.4 ± 12.5	21.2 ± 10.9	NS
Total sleep time (min)	325.8 ± 43.7	310.2 ± 75.5	NS
Sleep efficiency (%)	76.2 ± 4.1	69.8 ± 9.6	NS
% Stage 1 sleep	10.4 ± 2.0	13.1 ± 1.8	NS
% Stage 2 sleep	64.5 ± 2.6	60.8 ± 1.5	NS
% SWS	9.2 ± 2.3	7.3 ± 1.2	NS
% Stage REM sleep	15.9 ± 1.9	18.8 ± 1.4	NS
Microarousal index	10.6 ± 2.7	12.7 ± 1.5	NS
Apnea-hypopnea index	1.9 ± 2.1	2.4 ± 1.8	NS
PLMS index (n/h)	22.2 ± 16.5	10.2 ± 10.8	0.03

Data expressed as mean ± standard error of mean (SEM). SWS, slow wave sleep; REM, rapid eye movements; MA, microarousal; PLMS, periodic leg movements during sleep.

Table 4—Results of neuropsychological tests in patients with iRBD and controls at baseline

	RBD group (n = 24)	Controls (n = 12)	P
MMSE§	27.9 ± 2.9	28.3 ± 2.3	0.36
Memory			
Digit span forward§	5.6 ± 1.4	5.6 ± 1.4	0.48
Digit span backward§	3.5 ± 1.8	4.2 ± 0.9	0.67
Corsi block tapping task§	5.3 ± 1.4	5.3 ± 0.9	0.62
Corsi supraspan	12.0 ± 3.3	17.2 ± 5.9	0.025
Story recall	9.8 ± 5.1	14.0 ± 3.0	0.001*
Rey-Osterrieth complex figure delayed recall	15.9 ± 7.2	19.4 ± 5.3	0.07
Executive functions			
Raven's progressive matrices	32.4 ± 5.0	34.0 ± 2.8	0.34
Attentional matrices	47.8 ± 7.2	49.6 ± 5.4	0.48
Stroop color word interference test§	46.4 ± 25.0	35.3 ± 23.7	0.34
Trail Making Test (A)§	34.8 ± 21.7	17.8 ± 10.4	0.05
Trail Making Test (B)	46.9 ± 40.5	24.9 ± 31.2	0.19
Trail Making Test (B/A)	1.2 ± 0.7	2.2 ± 2.1	0.21
Phonemic fluency	33.7 ± 14.3	33.1 ± 5.2	0.89
Semantic fluency	40.3 ± 6.6	42.1 ± 6.5	0.46
Visuo-spatial abilities			
Rey-Osterrieth complex figure copy§	26.8 ± 7.7	33.1 ± 2.7	0.0005*

§Nonparametric test (Mann-Whitney U). *Significant P-values after adjusting for multiple testing ($\alpha < 0.0031$).

Table 5—Results of neuropsychological tests in patients with RBD and controls at follow-up

	RBD group (n = 24)	Controls (n = 12)	P
MMSE§	28.0 ± 1.9	28.3 ± 2.3	0.44
Memory			
Digit span forward§	5.4 ± 0.8	5.7 ± 1.4	0.89
Digit span backward§	4.0 ± 0.7	4.2 ± 0.8	0.24
Corsi supraspan	8.3 ± 2.8	18.3 ± 4.2	< 0.0001*
Story recall	7.9 ± 3.6	14.2 ± 2.3	0.0001*
Rey-Osterrieth complex figure delayed recall	14.8 ± 7.0	20.2 ± 4.4	0.02
Executive functions			
Raven's progressive matrices	30.7 ± 6.0	33.1 ± 2.2	0.23
Attentional matrices	46.6 ± 6.7	50.9 ± 5.3	0.07
Corsi block tapping task	4.7 ± 0.9	5.1 ± 0.7	0.21
Stroop color word interference test§	35.1 ± 25.4	35.3 ± 23.7	0.91
Trail Making Test A§	27.2 ± 15.8	17.8 ± 10.4	0.07
Trail Making Test B§	26.3 ± 46.9	24.9 ± 31.2	0.42
Trail Making Test B/A	0.6 ± 1.4	1.8 ± 2.2	0.09
Phonemic fluency	34.6 ± 11.3	36.4 ± 8.4	0.74
Semantic fluency	40.0 ± 6.5	43.7 ± 8.2	0.16
Visuo-spatial abilities			
Rey-Osterrieth complex figure copy	28.5 ± 5.3	34.9 ± 1.9	0.0004*

§Nonparametric test (Mann-Whitney U). *Significant P-values after adjusting for multiple testing (α < 0.0031).

mance than controls in delayed verbal memory (story recall: 9.8 ± 5.1 vs.14.0 ± 3.0; P = 0.001) and in visuo-constructional abilities (Copy of the Rey-Osterrieth complex figure: 26.8 ± 7.7 vs. 33.1 ± 2.7; P = 0.0005). After a mean follow-up period of 26.3 ± 5.0 months (range: 19-43 months), no patients complained of cognitive decline. However, 3 patients fulfilled the UK Brain Bank criteria for Parkinson disease.[37] At follow-up, the average BDI-II score was 9.6 ± 7.4 (range: 1-29), with 6 patients showing scores > 14, including 4 with scores > 20 (moderate depression). However, there was still no difference in mean BDI score between RBD patients and control subjects (mean BDI score in control subjects: 5.9 ± 4.2; P = 0.06). Seven patients at follow-up were taking clonazepam at bedtime. They were the same as in baseline plus 2 patients in which clonazepam was initiated after the first evaluation. The mean dose was 0.58 ± 0.27 mg, not significantly different from baseline (P = 0.94).

The results of the neuropsychological tests at follow-up are shown in Table 5. Patients with RBD not only still performed poorer than controls in the same tests as at baseline (story recall: 7.9 ± 3.6 vs.14.2 ± 2.3; P = 0.0001; Copy of the Rey-Osterrieth complex figure: 28.5 ± 5.3 vs. 34.9 ± 1.9; P = 0.0004), but they also showed an impairment in visuo-spatial learning (Corsi supraspan test: 8.3 ± 2.8 vs. 18.3 ± 4.2; P < 0.0001). Furthermore, ANOVAs showed a significant Group × Time interaction for Corsi supraspan scores ($F_{1,34}$ 7.36; P = 0.014), indicating a significant worsening of visuo-spatial learning over time in RBD compared to controls (P = 0.0001). A trend toward a significant Group × Time interaction for story recall ($F_{1,34}$ 3.87; P = 0.058) was also observed, suggesting a worsening in delayed verbal memory in RBD compared to controls. No significant Group × Time interactions were observed for the remaining neuropsychological tests

When comparing RBD patients who developed parkinsonism (symptomatic RBD, sRBD, n = 6) with those who remained idiopathic (iRBD, n = 21), no differences were observed in neuropsychological measures both at Baseline and Follow-up, although the small size does not allow a statistical comparison. Similarly, no differences in neuropsychological measures both at Baseline than at Follow-up were observed between RBD patients who were taking clonazepam and those who were drug free. Finally, no correlations were observed between neuropsychological functions that were impaired and age, disease duration, UPDRS-III score, and BDI-II score, either at baseline or at follow-up.

Number of subjects with abnormal scores in both RBD and control groups, at Baseline and at Follow-up, are reported in Table 6. At Baseline, abnormal scores were significantly more frequent in RBD patients than in control subjects in the story recall test (14 vs. 1; P = 0.005) and in the Rey-Osterreith complex figure copy test (20 vs. 1; P = 0.0001), while at Follow-up, differences in the frequency of abnormal scores between RBD and control subjects were observed in Corsi supraspan (14 vs. 1; P = 0.005), in the story recall test (20 vs. 2; P = 0.0002), and in the Rey-Osterreith complex figure copy test (15 vs. 0; P = 0.0003). The proportion of patients with RBD with impaired scores at follow-up did not increase significantly compared to that observed at baseline.

DISCUSSION

Neuropsychological deficits frequently occur in idiopathic RBD patients. The present study confirms the previously reported impairment in visuospatial functions (visuo-constructional abilities and visuo-spatial learning) in patients with idiopathic RBD, and in addition found a deficit in delayed recall. Indeed, an impairment in both visuo-constructional abilities, assessed by the copy of the Rey-Osterrieth complex figure test, and in delayed verbal memory, assessed by the story recall test, were observed in the majority of idiopathic RBD patients at Baseline (up to 19/24 and 20/24, respectively). Similar results, namely visuospatial and visuoconstructive deficits, as well as short-term memory impairment, have been found, in idiopathic RBD patients who developed a neurological disorder or had cognitive complaints after two years of clinical follow-up.[8] Visuoperceptual dysfunctions appear to be a marker of the disease. They typically occur also in early DLB, representing a distinctive feature when compared with AD.[17,18,21,38,39] Impairment of verbal memory is also reported in DLB and PD, although to a lesser degree than in AD.[40] Verbal memory was found impaired in idiopathic RBD patients in two previous studies, either with or without the co-occurrence of attention deficits.[13,14] The present study failed to find an attention impairment in patients with idiopathic RBD, although the lack of significance in some test, particularly the Trial Making test A and B, could be ascribed to the high variability of results.

Table 6—Number of subjects with pathological equivalent scores in each neuropsychological test

	RBD Baseline n = 24	Ctrls Baseline n = 12	P	RBD F-up n = 24	Ctrls F-up n = 12	P
MMSE§						
Memory						
Digit Span Forward§	2	0	NS	2	0	NS
Digit Span Backward§	9	3	NS	2	3	NS
Corsi block tapping task§	5	1	NS	5	1	NS
Corsi supraspan	9	2	NS	14	1	0.005
Story recall	14	1	0.005	20	2	0.0002
Rey-Osterrieth complex figure delayed recall	9	0	NS	9	0	0.02
Executive functions						
Raven's progressive matrices	3	0	NS	3	0	NS
Attentional matrices	2	0	NS	1	0	NS
Stroop color word interference test§	0	0	NS	0	0	NS
Trail Making Test (A)§	2	0	NS	0	0	NS
Trail Making Test (B)	0	0	NS	0	0	NS
Phonemic fluency	4	1	NS	4	1	NS
Semantic fluency	0	0	NS	1	0	NS
Visuo-spatial abilities						
Rey-Osterrieth complex figure copy§	19	1	0.0001	15	0	0.0003

§Non parametric test (Mann-Whitney U). RBD, REM behavior disorder; Ctrls, control subjects.

In addition our study indicates that cognitive dysfunction in idiopathic RBD progresses over time. After a mean period of approximately 2 years, a significant deterioration in visuo-spatial functions, namely visuo-spatial learning, was observed in patients with RBD compared to control subjects, since it slightly but consistently worsened in the majority of our iRBD patients. A trend toward a worsening in verbal memory was also observed. Visuo-constructional learning appears to be a domain that is particularly sensitive to deterioration in idiopathic RBD. In a previous study visuo-constructional learning abilities were also found to represent the most frequently impaired function in idiopathic RBD patients.[14] Based on these findings, it may be recommended that the Rey-Osterrieth complex figure delayed recall test should be included in the follow-up evaluation of idiopathic RBD patients

In our study, 3/24 patients (12.2%) fulfilled the UK Brain Bank criteria for PD at follow-up. Cognitive functions at baseline did not predict the eventual development of full-blown neurodegenerative disease, since no differences were observed at Baseline between patients who developed a symptomatic form of RBD and those who remained idiopathic. Furthermore, no relationship was observed between neuropsychological measures and UPDRS-III score. It was recently shown that patients with PD and concomitant RBD have a significant impairment in neuropsychological domains such as executive functions and visuo-spatial and visuo-perceptive abilities, compared to PD patients without RBD, and that the latter are no different from healthy subjects,[41] although that study did not take into account some important clinical variables linked to PD such as parkinsonian subtype. On the other hand, it was observed that the neuropsychological profile of patients with dementia and RBD, both with and without parkinsonism, was indistinguishable from that of probable DLB.[42] The results of the present study seems to support the notion that RBD is associated with subclinical or clinical cognitive deficits, regardless of the presence of parkinsonism.

If idiopathic RBD represents a preclinical stage of Lewy body disease, the finding of a cognitive impairment and its worsening, without evidence of motor signs in the majority of patients, would contrast with the stereotyped caudo-rostral pattern of progression of Lewy body pathology proposed by Braak et al. in Parkinson disease.[43] However, it is also known that motor signs become manifest only when a considerable proportion (e.g., 40% to 60%) of nigro-striatal dopaminergic neurons are lost.[44] It is therefore possible that cell loss in the substantia nigra would still occur earlier than in cortical areas, but perhaps progressing at a slower rate. Indeed, cognitive impairment in idiopathic RBD is often subtle and subclinical as well, as in this study patients were subjectively asymptomatic. However, it has to be pointed out that, in the present study, informants were not systematically queried about the cognitive performances of subjects and formal cognitive measures obtained by informants were not performed. This may represents an important limitation of the study, since anosognosia is observed to some degree in all neurodegenerative disorders which affect cognition.

Another possible limitation of this study was the fact that a subgroup of patients with RBD were taking clonazepam (n = 5 at baseline and n = 7 at follow-up), given the potential impact of benzodiazepines on daytime functioning and cognitive performances. However, all patients were on treatment at small doses from a mean period of 10.6 ± 7.8 months (range: 4-24 months). Furthermore, all patients treated at the time of the first evaluation were also treated at follow-up, with the exception of two additional patients at follow-up, and the mean dosage did not

change over time. Tolerance to the possible detrimental effects of benzodiazepines on cognitive functions has been described in long-term users of these drugs at higher doses than those observed in the present investigation.[45] Although it is not possible to exclude a negative effect of clonazepam on cognitive functions, it has to be pointed out that, when present, deficits in specific neuropsychological functions were observed in the vast majority of patients with RBD, and that no differences in cognitive performances were observed in our study between patients who were taking clonazepam and those who were not.

A possible objection might be the inclusion of subjects with mild depression indicated by BDI score ranging from 14 to 20. Furthermore, although there was no significant difference in mean BDI score between iRBD and control subjects at baseline, a trend toward a higher frequency of depressive symptoms was observed in patients with RBD compared to controls, both at baseline and at follow-up ($P = 0.062$ and 0.059, respectively). However, it is well known that depressive symptoms often precede by several years the clinical presentation of a full-blown neurodegenerative disorder,[46] possibly representing an early marker of an underlying neuropathological process, just as idiopathic RBD is. It may be argued that the presence of mild symptoms of depressions may have affected the cognitive performances in patients with RBD. However, the lack of correlation between BDI score and cognitive measures would not support this hypothesis, as well as, again, the fact that when present, neuropsychological deficits affected the vast majority of patients with RBD. It remains to be ascertained whether the slightly increase in depressive symptoms in patients with RBD reflects the impact of a chronic disease or an early sign of an impending neurodegenerative disease.

In summary, idiopathic RBD patients show neuropsychological deficits in visuo-spatial functions and in verbal memory, and those deficits progress over time. Deterioration in some cognitive domain, such as visuo-spatial learning, became significant after a relatively short period of follow-up, supporting the presence of an underlying degenerative process. A longer period of follow-up is needed to elucidate whether the presence of specific cognitive deficits in patients with RBD is predictive of the development of mild cognitive impairment and dementia.

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DISCLOSURE STATEMENT

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REFERENCES

1. Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. Sleep 1986;9:293-308
2. Schenck CH, Hurwitz T, Mahowald MW. REM sleep behaviour disorder: an update on a series of 96 patients and a review of the world literature. J. Sleep Res 1993;2:224-31.
3. Olson E, Boeve B, Silber M. Rapid eye movement sleep behavior disorder: demographic, clinical, and laboratory findings in 93 cases. Brain 2000;123:331-9
4. Schenck CH, Bundlie SR, Mahowald MW. Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder. Neurology 1996;46:388-93.
5. Boeve B, Silber M, Parisi J, et al. Synucleinopathy pathology and REM sleep behavior disorder plus dementia or parkinsonism. Neurology 2003;61:40-5.
6. Boeve B, Silber M, Ferman T, et al. Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy. Mov Disord 2001;16:622-30.
7. Schenck CH, Bundlie SR, Mahowald MW. REM behavior disorder (RBD): delayed emergence of parkinsonism and/or dementia in 65% of older men initially diagnosed with idiopathic RBD, and analysis of the minimum and maximum tonic and/or phasic electromyographic abnormalities found during REM sleep. Sleep 2003;26:Abstract Supplement: A316.
8. Iranzo A, Molinuevo JL, Santamaría J, et al. Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. Lancet Neurol 2006;5:572-7.
9. Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicotte-Marquez J, Montplaisir J. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. Neurology 2009;72:1296-1300.
10. Gagnon JF, Postuma RB, Mazza S, Doyon J, Montplaisir J. Rapid-eye-movement sleep behaviour disorder and neurodegenerative diseases. Lancet Neurol 2006 May;5:424-32.
11. Iranzo A, Lomeña F, Stockner H, et al. Decreased striatal dopamine transporter uptake and substantia nigra hyperechogenicity as risk markers of synucleinopathy in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study. Lancet Neurol 2010;9:1070-7.
12. Ferini-Strambi L, Di Gioia MS, Castronovo V, Oldani A, Zucconi M, Cappa SF. Neuropsychological assessment in idiopathic REM sleep behavior disorder (RBD). Does the idiopathic form of RBD really exist? Neurology 2004;62:41-5.
13. Massicotte-Marquez J, Décary A, Gagnon JF, et al. Executive dysfunction and memory impairment in idiopathic REM sleep behaviour disorder. Neurology 2008;70:1250-7.
14. Terzaghi M, Sinforiani E, Zucchella C, et al. Cognitive performance in REM sleep behaviour disorder: a possible early marker of neurodegenerative disease? Sleep Med 2008;9:343-51.
15. Gagnon J-F, Vendette M, Postuma RB, et al. Mild cognitive impairment in rapid eye movement sleep behavior disorder and Parkinson's disease. Ann Neurol 2009;66:39-47.
16. Molano J, Boeve B, Ferman T, et al. Mild cognitive impairment associated with limbic and neocortical Lewy body disease: a clinicopathological study. Brain 2010;133:540-56.
17. Salmon DP, Galasko D, Hansen LA, et al. Neuropsychological deficits associated with diffuse Lewy body disease. Brain Cogn 1996;31:148-65.
18. Mori E, Shimomura T, Fujimori M, et al. Visuoperceptual impairment in dementia with Lewy bodies. Arch Neurol 2000;57:489-93.
19. Ferman TJ, Boeve BF, Smith GE, et al. REM sleep behavior disorder and dementia: cognitive difference when compared with AD. Neurology 1999;52:951-7.
20. Ferman TJ, Boeve BF, Smith GE, et al. Dementia with Lewy bodies may present as dementia and REM sleep behavior disorder without parkinsonism or hallucinations. J Int Neuropsychol Soc 2002;8:907-14.
21. McKeith IG for the DLB Consortium. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863-72.
22. American Academy of Sleep Medicine. The international classification of sleep disorders, 2nd ed.: diagnostic and coding manual. Westchester, IL: American Academy of Sleep Medicine, 2005.
23. American Psychiatric Association. DSM-IV. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association, 1994.
24. Measso G, Cavarzeran F, Zappalà G, et al. The Mini-Mental state examination. Normative study of an Italian random sample. Dev Neuropsych 1991:9:77-85
25. Beck AT, Steer EA, Brown GK. The Beck Depression Inventory. 2nd ed. San Antonio, TX: The Psychological Corporation; 1996.
26. Fahn S, Elton RL, and Members of the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent developments in Parkinson's disease, vol. 2. Florham Park, NJ: Macmillan Health Care Information, 1987:153-64.

27. American Sleep Disorders Association. EEG arousal: scoring rules and examples. Sleep 1992;15:174-84.
28. Orsini A, Grossi D, Capitani E, Laiacona M, Papagno C, Vallar G. Verbal and spatial immediate memory span: normative data from 1355 adults and 1112 children. Ital J Neurol Sci 1987;8:539-48.
29. Spinnler H, Tognoni G. Taratura e standardizzazione italiana di test neuropsicologici. Ital J Neurol Sci 1987; Suppl. 8.
30. Mondini S, Mapelli D, Vestri A, Bisiacchi PS. L'esame neuropsicologico breve ENB. 2003, Raffaello Cortina, Milano, Italy.
31. Novelli G, Papagno C, Capitani E, Laiacona M, Cappa SF, Vallar G. Tre test clinici di memoria verbale a lungo termine. Taratura su soggetti normali. Arch Psicol Neurol Psichiatr 1986;2:278-96.
32. Capitani E, Laiacona M. Composite neuropsychological batteries and demographic correction: standardization based on equivalent score, with a review of published data. The Italian Group for the Neuropsychological Study of Ageing. J Clin Exp Neuropsychol 1997;19:795-809.
33. Caffarra P, Vezzadini G, Dieci F, Zonato F, Venneri A. Rey-Osterrieth complex figure: normative values in an Italian population sample. Neurol Sci 2002;22:443-47.
34. Giovagnoli AR, Del Pesce M, Mascheroni S, Simoncelli M, Laiacona M, Capitani E. Trail making test: normative values from 287 normal adult controls. Ital J Neurol Sci 996;17:305-9.
35. Lezak M. Neuropsychological assessment, 3rd ed. New York: Oxford University Press, 1995.
36. Calne DB, Snow BJ, Lee C. Criteria for diagnosing Parkinson's disease. Ann Neurol 1992;32(Suppl):125-7.
37. Litvan I, Bhatia KP, Burn DJ, et al. Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. Mov Disord 2003;18:467-86.
38. Tiraboschi P, Salmon DP, Hansen LA, Hofstetter RC, Thal LJ, Corey-Bloom J. What best differentiates Lewy body from Alzheimer's disease in early-stage dementia? Brain 2006;129:729-35.
39. Collerton D, Burn D, McKeith I, O'Brien J. Systematic review and meta-analysis show that dementia with Lewy bodies is a visual-perceptual and attentional-executive dementia. Dement Geriatr Cogn Disord 2003;16:229-37.
40. Metzler-Baddeley C. A review of cognitive impairments in dementia with Lewy bodies relative to Alzheimer's disease and Parkinson's disease with dementia. Cortex 2007;43:583-600.
41. Vendette M, Gagnon J-F, Décary A, et al. REM sleep behavior disorder predicts cognitive impairment in Parkinson disease without dementia. Neurology 2007;69:1843-9.
42. Boeve BF, Silber MH, Ferman TJ, et al. REM sleep behavior disorder and degenerative dementia: an association likely reflecting Lewy body disease. Neurology 1998;51:363-70.
43. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003;24:197-211.
44. Fearnley JM, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain 1991;114:2283-301.
45. Stewart SA. The effects of benzodiazepines on cognition. J Clin Psychiatry 2005;66 Suppl 2:9-13.
46. Shiba M, Bower JH, Marangore DM, et al. Anxiety disorders and depressive disorders preceding Parkinson's disease: a case-control study. Mov Disord 2000;15:669-77.