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ORIGINAL ARTICLE

Assessment of cognitive profile as a prodromal marker of the evolution of rapid eye movement sleep behavior disorder

Michele Terzaghi[1,2,*], Gianpaolo Toscano[1,2], Francesca Casoni[3], Marta Picascia[4], Dario Arnaldi[5,6], Valter Rustioni[1,2], Maurizio Versino[7], Elena Sinforiani[4] and Raffaele Manni[1]

[1]Unit of Sleep Medicine and Epilepsy, IRCCS Mondino Foundation, Pavia, Italy, [2]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, [3]Department of Clinical Neurosciences, IRCCS San Raffaele Scientific Institute, Milan, Italy, [4]Laboratory of Neuropsychology/Alzheimer's Disease Assessment Unit, IRCCS Mondino Foundation, Pavia, Italy, [5]Clinical Neurology, DINOGMI, University of Genoa, Genoa, Italy, [6]IRCCS Ospedale Policlinico San Martino, Genoa, Italy and [7]DMC University of Insubria, ASST Sette laghi Ospedale di Circolo, Varese, Italy

*Corresponding author. Michele Terzaghi, Sleep Medicine and Epilepsy Unit, IRCCS Mondino Foundation, Via Mondino, 27100 Pavia, Italy. Email: michele.terzaghi@mondino.it.

Abstract

Study Objectives: To search for a specific neuropsychological profile in idiopathic REM sleep behavior disorder (iRBD), able to predict the onset of neurodegenerative disorders.

Methods: In a longitudinal follow-up study of 63 consecutive iRBD patients (follow-up duration 6.7 ± 3.8 years), the baseline cognitive profile of converters to neurodegenerative disease was compared with that of the nonconverters. Five cognitive domains were assessed: memory, attention-working memory, executive functions, visuospatial abilities, language. Mild cognitive impairment (MCI) was diagnosed according to the Movement Disorder Society's diagnostic criteria for Parkinson's disease.

Results: 30 subjects (47.6%) developed a neurodegenerative disease (latency to conversion 60.33 ± 44.81 months). MCI was found in 50% of the converters and 12% of the nonconverters ($p = .001$), and its presence conferred a neurodegenerative disease risk of 10% at 3 years, 36% at 5 years, and 73% at 10 years ($p = .002$). Pathological equivalent scores on at least one neuropsychological test were detected in 46.7% of the converters versus 21.2% of the nonconverters in the memory domain ($p = .032$), in 40.0% versus 6.1% in that of executive functions ($p = .002$), and in 20.0% versus 3% in the visuospatial abilities domain ($p = .047$). On multivariate analysis, impaired executive functions significantly correlated with phenoconversion ($p = .018$). Lower Mini Mental State Examination (MMSE) scores ($p = .004$) and memory deficits ($p = .031$) were found in patients who developed dementia first.

Conclusions: Cognitive profile is useful for stratifying risk of phenoconversion in patients with iRBD. The presence of MCI and impaired executive functions, memory, and visuospatial abilities discriminated the converters. Lower MMSE scores and memory deficits may characterize those subjects who first develop dementia.

Statement of Significance

Many neurodegenerative biomarkers have been studied in idiopathic REM sleep behavior disorder (iRBD) to identify which individuals are at greater risk of developing a neurodegenerative disease. We confirm that cognitive profile characterization is a useful approach for stratifying the risk of phenoconversion in patients with iRBD. The presence of mild cognitive impairment (diagnosed according to the Movement Disorder Society's criteria) and of impaired memory, executive functions, and visuospatial abilities characterized our converters. Open questions with regard to the utility of neuropsychological assessment in iRBD are whether it can play an effective role in predicting which individuals are at risk of a worse cognitive outcome and whether the evolution of underlying deficits or new deficits during the course of the disease can be correlated with phenoconversion.

Key words: REM sleep behavior disorder; mild cognitive impairment; neurodegenerative disorders; Parkinson's disease; parkinsonism; neuropsychological assessment; phenoconversion risk

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Introduction

REM sleep behavior disorder (RBD) is a condition characterized by complex and often violent behaviors during sleep. It has a prevalence of 0.74%–1.06% in those over 60 in Western countries [1, 2]. More than 80% of patients with idiopathic RBD (iRBD) eventually develop a neurodegenerative disease, almost always a synucleinopathy (i.e. characterized by excessive accumulation of α-synuclein) [3].

Although several risk factors have been identified, no single test seems able to predict this phenoconversion [4–6]. Identification of predictors of conversion from iRBD to the various types of synucleinopathy is therefore a research priority.

Cross-sectional studies [7–9] and longitudinal studies [10–13] have shown, respectively, that cognitive performance is impaired in iRBD, and that they worsen over time, suggesting that they could play a role as prodromal markers. To date, however, no specific baseline neuropsychological profile in iRBD patients, associated with subsequent phenoconversion, has been identified.

From a cognitive perspective, a recent longitudinal study conducted in 76 subjects with iRBD showed at baseline assessments of the eventual converters a trend toward a higher rate of mild cognitive impairment (MCI) and worse performances on tests of attention and executive functions [13]. In detail, the baseline cognitive profile of the subjects who developed parkinsonism was found to be similar to that of the individuals who remained disease-free, whereas those who developed dementia more frequently had MCI at baseline (93% versus 42%) and showed impairment in all the cognitive domains explored, with changes in attention and executive functions reliably predicting the onset of dementia.

To investigate the potential of neuropsychological profiling as a means of predicting the development of dementia and/or parkinsonism, we conducted a longitudinal follow-up study in subjects initially diagnosed with iRBD. Given that formal criteria for the diagnosis of MCI in Parkinson's disease (PD) (MCI-PD) have already been established [14] and the final conversion point of iRBD almost invariably lies within the spectrum of Lewy body disorders, we thought it appropriate to adopt these criteria for evaluating MCI in our iRBD subjects.

Methods

Population and inclusion criteria

Data were collected from 67 consecutive patients diagnosed with iRBD according to the International Classification of Sleep Disorders, II and III editions. These patients were followed up for a minimum of 12 months (average follow-up duration 6.7 ± 3.8 years). Diagnosis and follow-up were performed at the sleep and epilepsy unit at the "C. Mondino" Neurological Institute, Pavia, Italy. Clinical, neurological, and neuropsychological evaluations were performed systematically at baseline and at regular follow-up visits. As part of these evaluations, the Unified Parkinson's Disease Rating Scale-part III (UPDRS-III) was administered to detect any subtle extrapyramidal motor symptoms.

The exclusion criteria that had been applied on diagnosing the patients with iRBD were: neurodegenerative disease or dementia, any neurological comorbidity (including epilepsy and narcolepsy), posttraumatic stress disorder, major depression, use of SSRIs and/or other antidepressant therapy, use of lithium or clonidine, and substance or alcohol abuse. Both at baseline and follow-up, dementia was defined as a cognitive decline from a previous level of performance sufficient to interfere with independence and resulting in the patients themselves, or their relatives, reporting impairment in any activity of daily living when administered the Instrumental Activities of Daily Living (IADL) scale [15].

Twelve of the included subjects had previously featured in other papers on this topic by our group [9, 11]: their data were updated and analyzed using the neuropsychological characterization and MCI definition criteria adopted in the present research. Follow-up duration was defined as the time that elapsed between the first neuropsychological evaluation and the clinical/neuropsychological evaluation at which the phenoconversion was established.

With regard to the clinical diagnoses, parkinsonism was diagnosed according to the UK Parkinson's Disease Society Brain Bank criteria for parkinsonism [16], dementia with Lewy bodies (DLB) according to DLB Consortium guidelines [17] and by consensus between a neurologist and a neuropsychologist, and multiple system atrophy (MSA) according to consensus criteria [18].

Eleven subjects had disordered breathing. This, however, showed no temporal relationship with RBD episodes on video-polysomnography and therefore allowed arousal-related "pseudo-RBD" to be excluded.

The local institutional review board approved the study and all subjects gave their informed consent prior to their inclusion.

Neuropsychological assessment

Each patient underwent a neuropsychological assessment performed by an experienced neuropsychologist (M.P.). This comprised [9, 11]:

- *MMSE*, to evaluate temporospatial orientation and obtain a general index of cognitive functioning [19];
- *Digit Span Forward*, *Word Span*, and *Corsi Test*, to evaluate short-term, verbal and spatial memory [20];
- *Attentive Matrices*, to investigate selective attention through visual search [20];
- *Rey 15-word Test*, with both immediate and delayed recall trials, to investigate long-term verbal memory for unstructured material [21];
- *Logical Memory*, which evaluates long-term verbal memory for structured material [20];
- verbal fluency, both phonemic and semantic (FAS) [21]
- *Weigl's Sorting Test* and *Frontal Assessment Battery* (FAB), which evaluate executive functions and abstract, categorical thinking [20, 22];
- *Raven's Colored Matrices 47*, which evaluates nonverbal logic [20];
- *Rey-Osterrieth Complex Figure (copy)* and *Constructive Praxia*, which evaluate copying skills [20, 23]
- *Rey-Osterrieth Complex Figure (delayed recall)*, which evaluates visuoconstructional learning abilities [23];
- *Sartori's Naming test* and *Word Comprehension* task, which evaluate language [24].

Data on subjective cognitive complaints reported by patients or by relatives/caregivers and scores on the IADL [15] scale, were systematically collected at baseline and at the follow-up visits.

The raw scores were used to calculate equivalent scores [25], which were considered pathological when equal to zero. In accordance with our previous studies on this topic [9, 11], for statistical purposes, all the tests were grouped into new variables ("domains") on the basis of the similarity of the evaluated functions. The following domains were thus defined: (1) memory (Rey-Osterrieth Complex Figure—delayed recall; Logical Memory; Rey 15-word Test immediate and delayed recall); (2) attention-working memory (Digit Span, Corsi Test, Word Span, Attentive Matrices); (3) executive functions (Raven's Colored Matrices 47; Weigl's Sorting Test; FAB; FAS); (4) visuospatial abilities (Constructive Praxia; Rey-Osterrieth Complex Figure—copy); (5) language: (Sartori's Naming test and Word Comprehension task). Each domain was coded as nonpathological or pathological according to the absence or presence of a pathological equivalent score on at least one of the instruments used to test the macrodomain.

Mild cognitive impairment

MCI and its subtypes were diagnosed using the Movement Disorder Society's criteria for the diagnosis of PD-MCI [14], namely the simultaneous presence of the following conditions: subjective cognitive complaints or suggestions of cognitive decline based on caregiver or clinician observation; objective evidence of cognitive decline, defined as an equivalent pathological score on at least two of the instruments used to test a given cognitive domain; preserved activities of daily living (assessed by the IADL scale). For a diagnosis of PD-MCI, impairment should be present on at least two neuropsychological tests, either within a single cognitive domain (single-domain MCI) or across different cognitive domains (multiple-domain MCI). MCI was not considered a neurodegenerative condition per se [7].

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, Baltimore, MD). Each variable was tested for normality using the Kolmogorov–Smirnov test. Means were compared using Student's *t*-test or the Mann–Whitney *U*-test for independent samples depending on the single variable distribution. Dichotomous variables were cross-tabulated in 2 × 2 tables and the chi-square test or the Fisher exact test was applied as appropriate. In order to assess the multicollinearity of the neuropsychological variables considered, a Spearman two-tailed correlation matrix was calculated. Multinomial logistic regression was used to test the association of single neuropsychological tests (coded as 0 = normal and 1 = pathological according to equivalent scores) with phenoconversion.

Logistic regression analysis was used to test multivariate effects, taking phenoconversion as the dependent variable and the following as covariates: age at diagnosis, age at cognitive testing, disease duration, and the different cognitive domains explored and found to be impaired (memory, attention-working memory, executive functions, visuospatial abilities; these were inserted in the model as binary variables and coded as 0 = normal and 1 = pathological according to equivalent scores). The acceptable level of significance was set at $p \leq .05$. To evaluate the cumulative incidence of phenoconversion, Kaplan–Meier survival analyses were conducted on the basis of the presence of MCI and pathological performances in single cognitive domains.

Results

Of the total 63 patients, 30 (47.6%) developed a neurodegenerative disease: PD in 19 cases, MSA in 4, and DLB in 7. They showed a mean latency to conversion of 60.33 ± 44.81 months (range 12–186; Table 1).

No sociodemographic or polysomnographic differences were found between the nonconverters and the converters. The converters showed a higher percentage of DAT SPECT abnormalities ($p = .04$).

The presence of MCI proved to be correlated with phenoconversion: MCI was found in 12% of the nonconverters and 50% of the converters ($p = .001$). No statistically significant difference was found between amnestic/nonamnestic forms of MCI and subsequent conversion. Single-domain MCI was found in three patients, two of whom showed impairment in the memory domain and one in the executive functions domain. Multiple-domain MCI was found in 16 patients, who showed simultaneous impairment in different combinations of domains: memory and attention-working memory ($n = 4$ patients); memory, executive functions, attention-working memory, and visuospatial abilities ($n = 3$); memory, executive functions, and visuospatial abilities ($n = 3$); memory and executive functions ($n = 3$); attention-working memory, executive functions, and visuospatial abilities ($n = 1$); memory and visuospatial abilities ($n = 1$); attention-working memory and executive functions ($n = 1$).

On analyzing the single cognitive domains explored, age- and education-equivalent scores [25] were found to be pathological on at least one test in 46.7% of the converters versus 21.2% of the nonconverters in the memory domain ($p = .032$), 40% versus 6% in the executive functions domain ($p = .002$), and 20% versus 3% in the visuospatial abilities domain ($p = .047$) (Table 2). On multivariate analysis, executive functions was the only domain showing a statistically significant correlation with phenoconversion ($p = .035$) (Table 3).

With regard to the single tests, significant differences were found between nonconverters and converters in their performances on the Rey 15-Word Test, both immediate and delayed recall (respectively, $p = .006$ and $p = .001$), and the Attentive Matrices ($p = .046$) and FAB ($p = .05$) (Table 2). The Spearman correlation matrix showed the substantial correlation between the above neuropsychological tests ($p = .01$); only FAB and Attentive Matrices were not correlated with each other. On multinomial logistic regression analysis, no single test showed a statistically significant association with phenoconversion.

Phenoconversion pattern: parkinsonism first versus dementia first

Of the 30 converters, 23 developed parkinsonism first and 7 dementia first (Table 4). Comparison of these two groups revealed statistically significant differences, with the dementia-first group showing lower MMSE scores ($p = .004$) and a greater frequency of impairment on at least one test from the memory domain ($p = .031$). No single test differed significantly between the patients who developed parkinsonism first and those who developed dementia first (Table 5).

Kaplan–Meier survival analyses

The risk of developing a neurodegenerative disease was 10% at 3 years from iRBD diagnosis, 36% at 5 years, and 73% at 10 years

Table 1. Baseline sociodemographic and clinical characteristics of iRBD patients

Variables	All iRBD (*n* = 63)	Disease free (*n* = 33)	Converted (*n* = 30)	P
Sex male n (%)	55 (87.3%)	31 (93.9%)	24 (80%)	.136*
Age at iRBD onset (years)	62.43 ± 8.32	61.93 ± 9.06	61.96 ± 7.57	.73†
Age at diagnosis (years)	66.46 ± 6.83	66.09 ± 7.48	66.87 ± 6.13	.66‡
Education	7.93 ± 3.89	7.93 ± 4.03	7.93 ± 3.81	1.00†
iRBD duration, subjective (years)	14.54 ± 19.05	14.03 ± 19.06	15.1 ± 19.36	.60†
iRBD duration at follow-up (months)	80.04 ± 45.58	69.69 ± 44.61	91.43 ± 44.61	.06‡
UPDRS-III	5.12 ± 5.18	4.37 ± 5.36	6.14 ± 4.87	.24‡
Latency to conversion (months)	—	—	60.33 ± 44.81	—
DAT SPECT deficit (%)	61.7	48.0	77.3	**.04***
MMSE corrected	26.13 ± 2.64	26.59 ± 2.41	25.62 ± 2.84	.176‡
MCI, *n* (%)	19 (30)	4 (12)	15 (50)	**.001***
Single domain, *n (%)*	3 (4.8)	1 (1.6)	2 (3.2)	**.004***
Multiple domain, *n (%)*	16 (25.4)	3 (4.8)	13 (20.6)	**.004***

Bold: statistically significant values.
*Chi-square Test; †Student *t*-test; ‡Mann–Whitney *U*-test.

Table 2. Pathological equivalent scores in RBD patients

	% All RBD (*n* = 63)	% Disease free (*n* = 33)	% Converted (*n* = 30)	P
Memory (at least one)	33.3%	21.2%	46.7%	**.032**
Rey 15-word test, immediate recall	17.4%	3.0%	30.0%	**.006**
Rey 15-word test, delayed recall	19.0%	3.0%	36.7%	**.001**
Logical Memory Test	11.1%	9.1%	13.3%	.700
Rey figure (delayed recall)	22.2%	12.1%	36.7%	.106
Attention and working memory (at least one)	19.0%	15.2%	23.3%	.525
Digit Span	3.2%	3.0%	3.3%	.945
Corsi Test	11.1%	9.1%	13.3%	.593
Word Span	6.3%	6.0%	6.6%	.943
Attentive Matrices	6.3%	0%	13.3%	**.046**
Executive Functions (at least one)	22.2%	6.0%	40.0%	**.002**
Raven matrices	12.7%	6.0%	20.0%	.141
Weigl's sorting test	15.9%	3.0%	26.7%	.263
FAB	30.1%	6.6%	46.7%	**.05**
FAS	7.9%	3.0%	13.3%	.183
Visuopatial abilities (at least one)	11.1%	3.0%	20.0%	**.047**
Constructive Praxia	3.2%	0%	6.7%	.205
Rey figure (copy)	17.5%	9.1%	26.6%	.200
Language (at least one)	0%	0%	0%	1
Sartori's naming test	0%	0%	0%	1
Sartori's word comprehension	0%	0%	0%	1

Percentages of patients recording pathological equivalent scores in each domain (at least one test impaired per domain) and on single tests are shown. Bold: statistically significant values (chi-square test).

Table 3. Multivariate analysis, showing statistically significant correlations between executive functions and RBD conversion

	Odds ratio	95% CI	P
Age at diagnosis	.908	0.634 –1.3	.462
Age at cognitive testing	1.058	0.751–1.489	.747
Disease duration	1.010	0.979 –1.042	.523
Executive functions	7.667	1.159 –50.711	**.035**
Memory	2.303	0.575 –9.218	.238
Visuospatial abilities	1.964	0.128 –30.065	.628
Attention and working memory	1.066	0.221 –5.143	.937

Bold: statistically significant values.

in subjects with MCI (single or multiple domain) compared with 6% at 3 years, 15% at 5 years, and 32% at 10 years in subjects without MCI (p = .002; Figure 1).

The risk conferred by having a pathological equivalent score on at least one of the instruments used to test a given domain (Figure 2) was 15% versus 0% at 3 years, 41% versus 13% at 5 years, and 91% versus 32% at 10 years (p = .001) for the executive functions domain; 6% versus 3% at 3 years, 27% versus 15% at 5 years, and 64% versus 39% (p = .049) at 10 years for memory; 17% versus 2% at 3 years, 48% versus 15% at 5 years, and 100% versus 40% at 10 years (p = .001) for visuospatial abilities; 0% versus 6% at 3 years, 22% versus 17% at 5 years, and 62% versus 43% at 10 years (p = ns) for attention-working memory.

Discussion

It has been shown that most patients with iRBD develop a neurodegenerative disease and that this risk increases over time: 25%–30% at 3 years, 33%–47% at 5 years, 66% at

Table 4. Baseline sociodemographic and clinical characteristics of RBD converters according to whether they developed parkinsonism or dementia first

	Parkinsonism first (*n* = 23)	Dementia first (*n* = 7)	P
Sex, *n* male (%)	18 (78.3)	6 (85.7)	.666*
Age at RBD onset (years)	62.43 ± 7.90	64.71 ± 6.62	.495†
Age at diagnosis (years)	66.82 ± 5.79	67.00 ± 7.65	.949†
Education	8.21 ± 4.04	7.00 ± 3.00	.36†
RBD duration, subjective (years)	16.34 ± 22.05	11.00 ± 2.00	.532†
RBD duration at follow-up (months)	86.95 ± 46.86	106.14 ± 35.15	.328†
UPDRS-III	6.56 ± 4.91	4.80 ± 5.02	.494†
Latency to conversion (months)	53.57 ± 41.36	82.57 ± 50.97	.136†
DAT deficit (%)	73.3	85.7	1.00*
MMSE corrected score	26.46 ± 2.27	22.86 ± 2.92	**.004†**
MCI, *n* (%)	10 (43.5)	5 (71.4)	.39*
Single domain, *n* (%)	2 (8.7)	0 (0)	.21*
Multiple domain, *n* (%)	8 (34.8)	5 (71.4)	.21*

Bold: statistically significant values.
*Fisher exact test; †Mann–Whitney *U*-test.

Table 5. Pathological equivalent scores in RBD patients who converted first to Parkinsonism or to dementia

	Parkinsonism first % (*n* = 23)	Dementia first % (*n* = 7)	P
Memory (at least one)	34.8%	85.7%	**.031**
Rey 15-word test, immediate recall	21.7%	57.1%	.153
Rey 15-word test, delayed recall	26.1%	71.4%	.068
Logical Memory Test	8.7%	28.5%	.225
Rey figure (delayed recall)	21.7%	28.5%	1.0
Attention and working memory (at least one)	26.1%	14.3%	1.0
Digit Span	4.3%	0%	1.0
Corsi Test	13.0%	14. 3%	1.0
Word Span	8.7%	0%	1.0
Attentive Matrices	8.7%	28.6%	.225
Executive functions (at least one)	30.4%	71.4%	.084
Raven matrices	8.7%	57.1%	.16
Weigl's sorting test	21.7%	28.6%	1.0
FAB	30.4%	100%	.07
FAS	8.7%	28.6%	.225
Visuospatial abilities (at least one)	17.4%	28.6%	.603
Constructive Praxia	4.3%	14.3%	.402
Rey figure (copy)	26.0%	42.8%	.505
Language (at least one)	0%	0%	1
Sartori's naming test	0%	0%	1
Sartori's word comprehension	0%	0%	1

Bold: statistically significant values (Fisher exact test).

7.5 years, 76% at 10 years, and 81%–91% at 14 years [3, 6, 26, 27]. Multicenter studies published to date have shown a 17.9%–25% risk at 3 years [6, 28], rising to 31%–41% at 5 years [6, 28], 60% at 10 years, and 73% at 12 years [28]. Although several prodromal markers of neurodegeneration have been identified in iRBD, no single test seems able to predict this phenoconversion. The lack of biomarkers of evolution of the disease, particularly into dementia, represents a significant clinical gap.

We conducted a prospective study of 63 iRBD subjects submitted to homogeneous neuropsychological evaluation at a mean follow-up of 6.7 years. Adopting the Movement Disorder Society's five-domain criteria for diagnosing PD-MCI [14], we found that the iRBD subjects who converted to a neurodegenerative disease more frequently had MCI at baseline, predominantly the multiple-domain subtype (including both amnestic and nonamnestic forms). Different MCI subtypes have indeed been described in iRBD, ranging from single-domain involvement to types affecting all domains [7, 9, 13]. Although the small sample size undoubtedly reduced the statistical power of our study, our data did not show different subtypes of MCI to be associated with differences in the average time to phenoconversion or in the evolution of the cognitive profile (dementia versus non dementia). About one-third of our subjects had MCI at baseline. This proportion is in line with the data from the literature: in a population-based study, 32% of cognitively intact subjects with iRBD developed MCI after a median of 3.8 years [29], while data from sleep centers detected a higher risk, up to 50%–65% versus 8% in healthy subjects [8].

Data from the literature show that MCI can progress over time [11] and follow-up data have shown that up to 93% of patients with RBD plus MCI develop dementia after an average of 3.6 years [13]. However, in iRBD as well as in

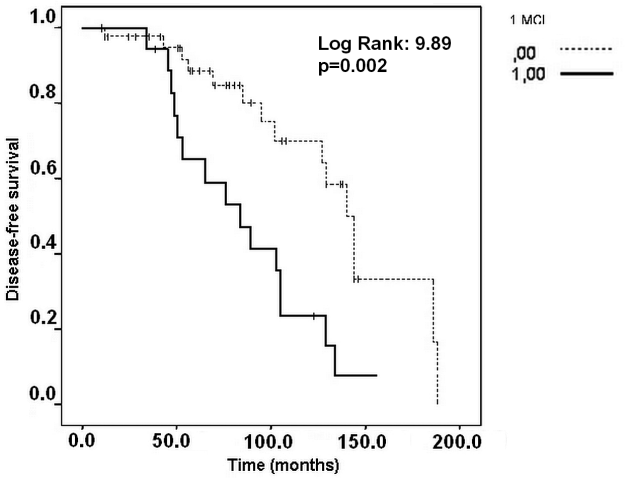

Figure 1. Cumulative survival analysis of neurological disease-free idiopathic RBD by Kaplan–Meier's method based on MCI diagnosis.

the general population, MCI does not always evolve into a neurodegenerative disorder [11]. Studies combining MCI with other biomarkers of impending degeneration in iRBD are needed to clarify whether MCI is actually a precursor of neurodegenerative diseases.

Clarification of this aspect would also make it possible to establish whether iRBD plus MCI represents a more severe phenotype than cognitively intact iRBD. This suggestion is supported by numerous findings described in iRBD-plus-MCI patients, who have been reported to show greater cortical thinning in the frontal, cingulate, temporal, and occipital regions and subcortical abnormalities in the lenticular nucleus and thalamus compared with iRBD patients without MCI [30]. Moreover, on DAT SPECT imaging, iRBD-plus-MCI patients have also been found to show an abnormal pattern of brain perfusion, characterized by relatively reduced perfusion in the occipital, temporal, and parietal regions and relatively increased perfusion in the right hippocampus, putamen, and left paracentral gyrus [31]. In addition, electroencephalographic (EEG) slowing has been described in subjects with iRBD who developed MCI: patients who, after an

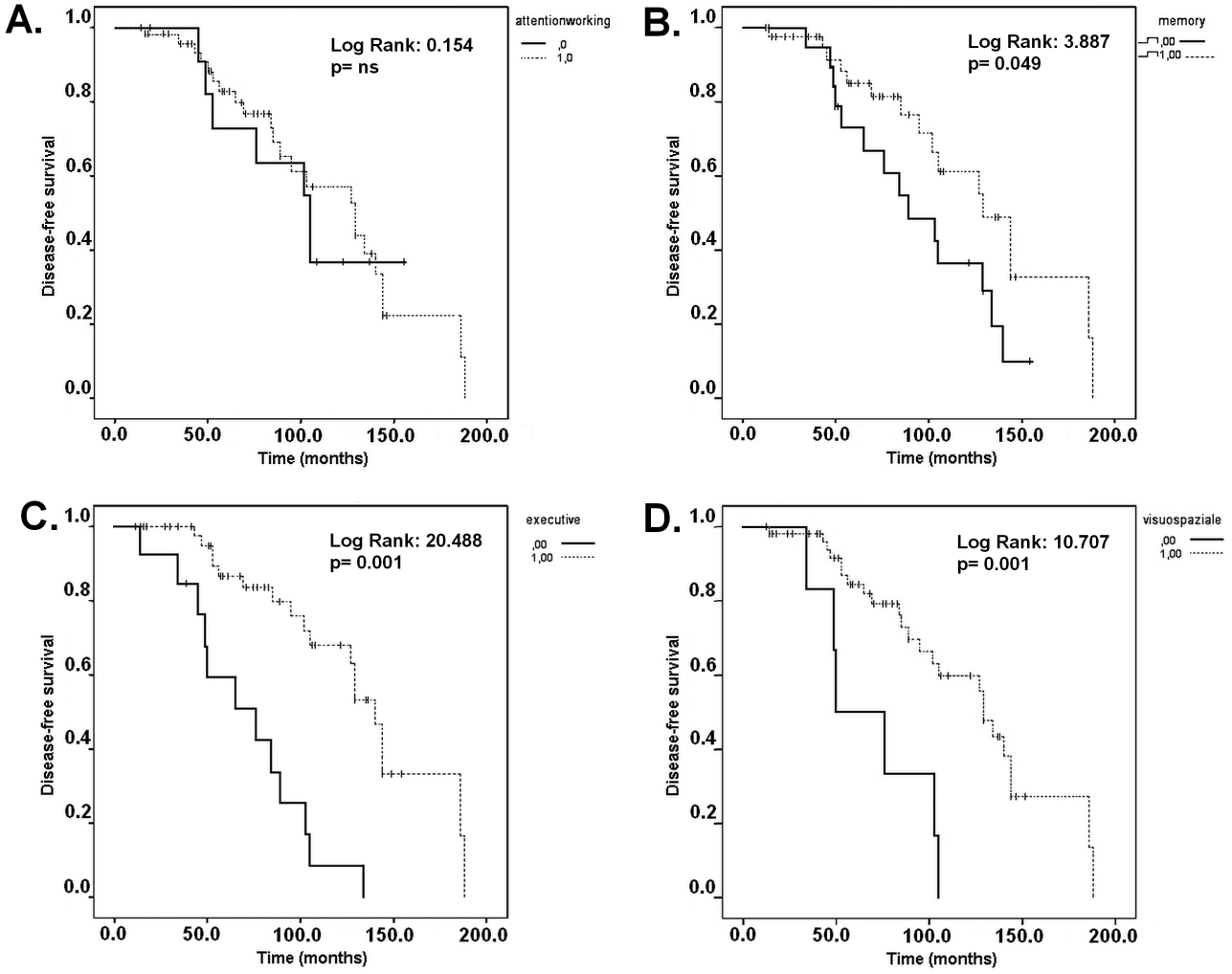

Figure 2. Survival analysis of neurological disease-free idiopathic RBD by Kaplan–Meier's method based on (A) attention and working memory deficits; (B) memory deficits; (C) executive function deficits; and (D) visuospatial deficits.

average clinical follow-up of 2.40 ± 1.55 years, were diagnosed with MCI had a marked slowing of EEG activity in central and occipital derivations during wakefulness and REM sleep compared with controls and MCI-free patients [32].

All in all, these findings suggest that the presence of MCI in iRBD indicates a more severe neuroimaging and neurophysiological phenotype and that iRBD plus MCI might possibly constitute a subentity within iRBD. Studies on cognition in iRBD have shown that visuospatial abilities are the most frequently affected domain, with alterations in short- and long-term memory, attention, executive functions, and decision-making also reported to be impaired in iRBD [9–12, 28, 33, 34]. Subjects who converted to a neurodegenerative disorder have been reported to show lower standardized z-scores in executive functions (i.e. Trail Making Test A–mean follow-up 50.84 ± 25.38 months) at baseline [12]. Our data confirm the presence of impaired performance on at least one test of memory, executive functions, and visuospatial abilities, while the results of our multivariate analysis highlight the role of the executive deficit. Thus, we confirm that subjects with impaired executive functions, as well as those with MCI, should be closely monitored for conversion, as already suggested by Youn *et al.* [12]

At the single test level, we found that performances on the Rey 15-Word Test, both immediate and delayed recall, Attentive Matrices and FAB were more frequently impaired in iRBD subjects who converted to neurodegenerative diseases; a certain degree of collinearity was found to be present between these tests. Multinomial logistic regression analysis identified no single variable able to predict phenoconversion. Recently, a prospective study in 76 subjects with iRBD, 34 of whom developed a neurodegenerative disease after an average follow-up of 3.6 ± 2.4 years, found that subjects who first developed dementia (15 subjects) more frequently showed impairments in attention/executive functions, learning/memory, and visuospatial abilities, as well as a higher frequency of MCI compared with the parkinsonism-first group (19 subjects) [13]. Pathological scores on tests of attentive and executive functions (Stroop Color Word Test and Trail Making Test, parts A and B) predicted dementia in iRBD. No cognitive difference was found between parkinsonism-first subjects and nonconverters [13].

We found lower MMSE scores and a higher frequency of memory deficits in our dementia-first subjects but found no other differences at baseline between dementia-first and parkinsonism-first subjects. This could be due to an unbalanced sample in which the rate of parkinsonism was more than three times higher than that of dementia: 23 versus 7 as opposed to 19 versus 15 in the study by Marchand *et al.* [13]. Indeed, compared with Marchand *et al.* [13], we had fewer converters to dementia to evaluate (11.1% versus 19.7%), despite our longer follow-up (6.7 ± 3.8 versus 3.6 ± 2.4 years); this small number of subjects with dementia may have limited the statistical power of our study.

A further limitation of our research derives from the fact that while we analyzed the baseline neurocognitive profile of our patients in order to assess phenoconversion, we failed to study this profile longitudinally and were therefore unable to evaluate the potential of dynamic changes as possible markers of prodromal synucleinopathies. Indeed, it has been shown that while some deficits remain stable over time, further cognitive impairment, mainly involving nonverbal logic, attention, executive functions [11], and working memory [12], can be observed in the follow-up of iRBD [35,36]. It has been shown that cognitive deficits progress differently between subjects who first develop dementia as opposed to parkinsonism [35]: in the former, verbal episodic learning and memory deficits started later than deficits in attention and executive functions and a more severe general decline in cognitive performance was found. The potential of this dynamic as a predictor of phenoconversion seems to be noteworthy, but it remains to be ascertained whether the evolution of underlying deficits or new deficits appearing during the course of iRBD can be correlated with phenoconversion.

Concluding Remarks

iRBD is a heterogeneous condition: some subjects continue to display "idiopathic" forms for many years, while others develop synucleinopathies in the space of just a few years. Our follow-up study of patients with iRBD supports the view that cognitive characterization may provide a useful tool for stratifying patients according to their risk of phenoconversion. The presence of multiple-domain MCI and impaired performance in the executive, memory, and visuospatial abilities domains could identify iRBD subjects who will go on to develop a synucleinopathy. A lower MMSE score and memory deficits can potentially distinguish subjects who will first develop dementia from those whose condition will first evolve toward parkinsonism. Further studies analyzing the relationship between different MCI subtypes and phenoconversion could identify new neuropsychological markers able to predict evolution. In the same way, longitudinal studies of the evolution of underlying deficits or new deficits appearing during the course of iRBD could contribute to prediction of the ultimate outcomes of the disease process.

Further study of the cognitive profile of iRBD, once standardization of neuropsychological testing has been achieved, may improve our ability to stratify iRBD subjects risk of conversion and to predict their type of evolution and therefore ultimately lead to better criteria for inclusion in future, disease-modifying clinical trials.

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