



Influence of RBD onset on the clinical characteristics of Parkinson's disease patients: a retrospective study

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Abstract

Introduction In Parkinson's disease (PD), rapid eye movement (REM) sleep behavior disorder (RBD) might either precede the appearance of motor symptoms, or develop during the disease course. PD patients with RBD are characterized by a higher burden of cognitive impairment and hallucinations. However, few studies have analyzed the clinical characteristics of PD patients according to the timeline of RBD onset.

Methods PD patients have been retrospectively enrolled. Presence and onset of probable RBD (pRBD) has been evaluated using RBD Screening Questionnaire (score ≥ 6). Presence of Mild Cognitive Impairment (MCI) at baseline has been evaluated using the MDS criteria level II. Presence of motor complications and hallucinations has been evaluated at a 5-year follow-up.

Results A total of 115 PD patients (65 men, 56.5%; mean age 62.5 ± 9.7 years; mean disease duration 3.7 ± 3.9 years) have been enrolled. Out of these, 63 fulfilled the diagnosis of pRBD (54.8%) with 21 (33.3%) reporting the RBD onset before the onset of the motor symptoms (PD-RBDpre), and 42 (66.7%) after the motor symptoms (PD-RBDpost). At enrolment presence of MCI was associated with PD-RBDpre patients (OR 5.04; 95% CI 1.33–19.05; p value 0.02). At follow-up, a higher risk of developing hallucinations was also associated with PD-RBDpre (OR 4.68; 95% CI 1.24–17.63; $p = 0.022$).

Conclusions PD patients with RBD occurring before the onset of motor symptoms represent a subgroup of patients with a more severe cognitive phenotype and with a higher risk of developing hallucinations along the disease course, with significant implications in terms of prognostic stratification and therapeutic approach.

Keywords Parkinson's disease · REM sleep behavior disorder · Cognitive impairment · Hallucinations

Introduction

PD is a neurodegenerative disease characterized by the presence of both motor and non-motor symptoms such as cognitive impairment, depression, hallucinations and sleep disorders.

Rapid Eye Movement (REM) Sleep Behavior Disorder (RBD) is one of the most frequent sleep disorders in PD, with up to 42.5% of prevalence in PD patients [1] and is characterized by the presence of abnormal behaviors during

REM sleep including kicking, shouting and the production of complex movements. When present, RBD is associated with a more severe disease phenotype, including a higher prevalence of cognitive impairment and hallucinations, impacting the prognosis and quality of life of these patients [2, 3]. On the other hand, RBD, in its isolated form, has a low prevalence on the general population [4] and is also considered a prodromal neurodegenerative disease, harboring the future development of an alphasynucleinopathy (either PD or Lewy Body Dementia or Multiple System Atrophy), with the onset up to 30 years before the development of motor symptoms [5, 6] and an estimated risk of phenoconversion to an overt alpha-synucleinopathy of 6.25% yearly [7]. Moreover, isolated RBD (iRBD) patients display a higher burden of parkinsonian non-motor symptoms, including cognitive impairment [8]. Considering RBD as the most relevant non-motor symptom of PD, a recent multimodal imaging study has thus suggested to classify PD into a “body first” phenotype,

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where the disease starts in the peripheral autonomic nervous system and slowly reaches the brainstem and the cortical areas, and a “brain first” phenotype, where the disease starts in the central nervous system and then spreads towards the brainstem [9]. As such, “body first” PD should be clinically characterized by a preponderance of non-motor symptoms along with isolated RBD and the subsequent development of PD motor symptoms; on the other hand, “brain first” PD should represent a more classical PD phenotype with the eventual development of RBD along the disease course [9], despite not all PD patients will develop RBD.

Up to date, few studies have addressed the difference in clinical characteristics of PD patients on the basis of RBD onset, generally finding a longer disease duration and worse motor performances in “brain first” phenotype [10, 11], or no differences [12]. The aim of our study is to compare the clinical and cognitive characteristics of PD patients based on the onset of RBD, and to assess the risk of future development of motor complications and hallucinations.

Materials and methods

Study population

Non-demented patients diagnosed with Parkinson's disease according to the United Kingdom Brain Bank criteria [13] between 2012 and 2018 were recruited from the Parkinson's Disease and Movement Disorders Outpatient Clinic of the Azienda Ospedaliero Universitaria Policlinico “G. Rodolico-San Marco”. At the time of the enrollment (first referral visit), motor assessment was performed on OFF state. Motor impairment was evaluated using the Unified Parkinson's Disease Rating Scale-Motor examination (UPDRS-ME). For patients already on treatment with levodopa or other dopaminergic drugs, the levodopa equivalent dose (LED) has been calculated. Presence of sleepiness has been recorded at baseline as part of the standard semi-structured interview. The drugs used for the treatment of RBD (clonazepam and melatonin) have also been recorded. Follow-up (FU) routine clinical examinations data have been retrospectively gathered at 5 years after the baseline. At follow-up evaluation, presence of hallucinations has been scored using UPDRS I and presence of motor complications (dyskinesias and wearing-off) using the UPDRS IV.

Diagnosis of RBD

Presence of RBD has been evaluated at the time of the enrolment (first referral visit) on the basis of the clinical history. PD patients presenting RBD at baseline were asked whether this disorder had occurred previously or at least 1 year after the onset of PD motor symptoms. Patients who

developed RBD before PD motor onset were classified as PD-RBDpre, while patients who developed RBD at least 1 year after PD motor onset as PD-RBDpost. Those patients who did not present RBD at baseline, but developed RBD during the FU were classified as PD-RBDpost. On the other hand, PD patients free of RBD at the last FU were considered as RBD negative (PD-RBD-). For the purposes of this study, diagnostic confirmation of PD-RBD cases has been conducted during follow-up examinations administering the Italian validated version of the REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) to both patients and bed partners [14] considering a score ≥ 6 as cutoff for the diagnosis of probable RBD (pRBD) [15].

Neuropsychological assessment

At baseline, all the enrolled patients underwent a comprehensive neuropsychological assessment when in “on” state. Patients underwent the evaluation of global cognition using the following tests: the Mini Mental State Examination (MMSE), and the Frontal Assessment Battery (FAB). Presence of depression has been assessed using the Hamilton Depression Rating Scale (HDRS). According to MDS Level II criteria [16], Mild cognitive impairment (MCI) was diagnosed when patients scored below the cut-off values in at least two neuropsychological tests. The memory domain has been assessed with the Rey's Auditory Verbal Learning Test and the Prose recall test with a delayed recall condition; the attention domain with the Stroop color-word test and the Trail Making Test part A; the executive function domain with the Verbal fluency letter test (COWAT) and the Colored Raven's Progressive Matrices; the visuo-spatial function domain with the Clock drawing test (CDT) and the Copy of figures. For each test, administration procedures and Italian normative data for score adjustment (based on age, gender and education) were used. Neuropsychological performances were considered as impaired when the subject scored 2 standard deviations (SD) below normality cut-off values. A domain was defined as impaired if at least one of the cognitive tests of the specific domain was altered.

Statistical analysis

Data have been entered in an ad hoc created database. At baseline, quantitative variables have been compared using the Student's *t* test or Wilcoxon rank test when appropriated. Qualitative variables have been analyzed using Chi-squared or Fisher's exact test when appropriate. In order to test the strength of association between study outcomes and the presence of RBD, a univariate and multivariate logistic regression analysis has been performed. For the baseline cognitive outcomes (presence of MCI, impaired subdomains), the multivariate models were adjusted for age at

baseline, disease duration, sex, UPDRS-ME and education. Whereas, FU outcomes (presence of hallucinations, dyskinesias, wearing-off) models have been adjusted for sex, age at FU, disease duration at FU and LED at FU. For the outcome hallucinations, the models were adjusted also for the use of dopamine agonists (DA). Analyses have been conducted comparing PD-RBD- vs PD-RBD+ patients and then stratifying PD-RBD+ patients in PD-RBDpre and PD-RBDpost.

Results

Baseline characteristics

A total of 115 PD patients (65 men, 56.5%; mean age 62.5 ± 9.7 years; mean disease duration 3.7 ± 3.9 years; UPDRS-ME 28.9 ± 11.5) have been retrospectively enrolled. All the enrolled patients underwent the RBDSQ administration with the help of the bed partner or the caregiver. Out of these 115 at the time of the enrolment, 52 (45.2%) did not present RBD, while 63 fulfilled the diagnosis of pRBD (54.8%). Out of these 63 PD-RBD patients,

21 (33.3%) reported the RBD onset before the onset of the motor symptoms (PD-RBDpre), while 42 (66.7%) after the motor symptoms (PD-RBDpost).

Baseline characteristics were not significantly different between PD patients with and without RBD, except for a higher mean LED among PD-RBD+ patients (248.4 ± 426.1 mg), a higher HDRS score (8.1 ± 5.4) and a higher frequency of MCI (41.3% vs 21.1%) (Table 1). On the other hand, PD-RBDpost presented a significantly longer disease duration with respect PD-RBDpre (4.9 ± 4.8 years versus 2.7 ± 2.0 years; p value 0.05), a younger age at enrolment (60.9 ± 9.2 years vs 66.7 ± 9.0 years; p value 0.03), and at onset (57.7 ± 9.8 years versus 64.0 ± 8.8 years; p value 0.01), while also having a significantly longer disease duration at the last follow-up (12.7 ± 7.4 years versus 8.0 ± 2.6 years; p value 0.007) as shown in Table 1. At baseline, only six patients (5.2%) were taking clonazepam, four of them were diagnosed as PD-RBDpre, one as PD-RBD- and another as PD-RBDpost. The latter two patients were on medication for the presence of comorbid anxiety. None of the patients were taking melatonin at baseline examination.

Table 1 Baseline characteristics

	PD-RBD-, (n=52)	PD-RBD+, (n=63)	PD-RBDpre (n=21)	PD-RBDpost (n=42)	<i>p</i> value RBD+ vs RBD-	<i>p</i> value PD-RBDpre vs PD-RBDpost
Age (basal), mean \pm SD	62.2 ± 10.2	62.8 ± 9.4	66.7 ± 9.0	60.9 ± 9.2	0.8	0.03
Age (last follow-up), mean \pm SD	68.9 ± 9.7	69.8 ± 9.3	71.9 ± 8.3	68.7 ± 9.7	0.6	0.2
Sex(men), <i>n</i> (%)	27 (51.9)	38 (60.3)	13 (61.9)	25 (59.5)	0.4	0.8
Age at onset, mean \pm SD	59.6 ± 10.9	59.8 ± 9.9	64.0 ± 8.8	57.7 ± 9.8	0.9	0.01
Disease duration (basal), mean \pm SD	3.1 ± 3.5	4.1 ± 4.2	2.7 ± 2.0	4.9 ± 4.8	0.2	0.05
Disease duration (last follow-up), mean \pm SD	9.8 ± 5.6	11.1 ± 6.5	8.0 ± 2.6	12.7 ± 7.4	0.2	0.007
Education, mean \pm SD	9.8 ± 3.8	9.2 ± 4.1	9.6 ± 4.5	9.0 ± 4.0	0.5	0.6
UPDRS-ME, mean \pm SD	28.1 ± 11.6	29.6 ± 11.6	28.3 ± 9.5	30.2 ± 12.6	0.5	0.5
MMSE, mean \pm SD	27.2 ± 2.1	27.2 ± 2.5	27.3 ± 3.1	27.2 ± 2.2	0.9	0.9
FAB, mean \pm SD	14.6 ± 2.7	14.8 ± 2.5	14.2 ± 2.9	15.0 ± 2.3	0.7	0.2
HDRS, mean \pm SD	5.5 ± 5.14	8.1 ± 5.4	8.9 ± 4.4	7.7 ± 5.8	0.01	0.4
Sleepiness, <i>n</i> (%)	3 (5.8)	7 (11.1)	2 (9.5)	5 (11.9)	0.5	1
MCI, <i>n</i> (%)	12 (23.1)	26 (41.3)	12 (57.1)	14 (33.3)	0.03	0.08
LED baseline, mean \pm SD	115.9 ± 237.4	248.4 ± 426.1	104.3 ± 291.5	320.5 ± 465.9	0.047	0.056

In bold significant *p* values

UPDRS-ME Unified Parkinson's Disease Rating Scale-Motor Examination, MMSE Mini Mental State Examination, FAB Frontal Assessment Battery, HDRS Hamilton Depression Rating Scale, MCI mild cognitive impairment, LED levodopa equivalent dose, SD standard deviation

Cognitive function and RBD

We did not find any significant difference concerning the FAB and MMSE score between PD patients with and without RBD as well as between RBD pre and post. Nonetheless, considering the presence of MCI, diagnosed according the MDS criteria level II, at univariate analysis, we found a positive significant association between MCI and presence of RBD (OR 2.49; 95% CI 1.09–5.70; *p* value 0.03) and a close even if not significant association was found a multivariate analysis, as shown in Table 2. However, when analysis was stratified considering the timing of onset of the RBD (RBDpre and RBDpost) at multivariate analysis, a stronger and significant association was found only for those PD patients who had had the onset of RBD before the onset of the motor symptoms (PD-RBDpre OR 5.04; 95% CI 1.33–19.05; *p* value 0.02), while no association has been found for the PD-RBDpost as shown in Table 2. At multivariate analysis, no association has been found between RBD and the single domains investigated (Table 2). At univariate

analysis, treatment with clonazepam was significantly associated with presence of MCI (OR 10.60; 95% CI 1.19–94.44; *p* value 0.03). Nonetheless, when included in the multivariate model clonazepam was no longer associated with MCI and did not modify the strength of association between MCI and presence of RBD. Finally, HDRS and sleepiness were not associated with MCI as well as with the single domains at both univariate and multivariate analysis.

Follow-up at 5 years

Out of the 115 PD patients, 97 (57 men 58.8%; mean age at FU 67.2 ± 9.4 years) had a follow-up visit after 5 years from the baseline. Of these 97 PD patients, 41 were RBD- (42.3%), while 56 (57.7%) presented RBD (19 [19.6%] were PD-RBDpre and 37 [38.1%] PD-RBDpost). Thirty-six of them reported the presence of visual hallucinations (37.1%), 32 (33.3%) dyskinesias and 36 (37.1%) wearing-off. At the univariate analysis, excluding the patients who reported the presence of hallucinations at baseline (*n* = 5) we found a

Table 2 Cognitive function and RBD at baseline: univariate and multivariate analysis

	Univariate analysis			Multivariate analysis		
	OR	95% CI	<i>p</i> value	adjOR	95% CI	<i>p</i> value
Memory						
PD-RBD+	1.20	0.52–2.76	0.7	0.85	0.31–2.34	0.7
PD-RBD-	1	/	/	1	/	/
PD-RBDpre	2.72	0.94–7.88	0.06	1.92	0.52–6.99	0.3
PD-RBDpost	0.70	0.26–1.90	0.5	0.44	0.12–1.56	0.2
Attention						
PD-RBD+	2.22	0.90–5.42	0.08	2.41	0.86–6.70	0.09
PD-RBD-	1	/	/	1	/	/
PD-RBDpre	3.58	1.16–11.02	0.02	2.89	0.81–10.19	0.1
PD-RBDpost	1.69	0.63–4.58	0.3	2.09	0.64–6.81	0.2
Visuospatial						
PD-RBD+	1.20	0.48–2.98	0.7	0.66	0.20–2.13	0.4
PD-RBD-	1	/	/	1	/	/
PD-RBDpre	2.1	0.67–6.56	0.2	1.64	0.40–6.62	0.5
PD-RBDpost	0.84	0.29–2.44	0.7	0.25	0.04–1.27	0.09
Executive						
PD-RBD+	0.92	0.40–2.12	0.8	0.65	0.24–1.71	0.3
PD-RBD-	1	/	/	1	/	/
PD-RBDpre	0.85	0.261–2.75	0.8	0.56	0.14–2.11	0.4
PD-RBDpost	0.96	0.38–2.41	0.9	0.71	0.23–2.13	0.5
MCI						
PD-RBD+	2.49	1.09–5.70	0.03	2.01	0.77–5.22	0.152
PD-RBD-	1	/	/	1	/	/
PD-RBDpre	4.75	1.57–14.3	0.006	5.04	1.33–19.05	0.02
PD-RBDpost	1.77	0.70–4.46	0.2	1.15	0.37–3.52	0.8

In bold significant *p* values

AdjOR OR Adjusted by education, age at baseline, disease duration, sex, UPDRS-ME, 95% CI 95% confidence intervals

positive, but no significant association with the presence of RBD (OR 2.25; 95% CI 0.9–5.6; p value 0.08), even when adjusting by confounding variables (sex, use of dopamine agonists, LED, age at FU and disease duration at FU). Concerning motor complications, at univariate analysis no association was found for both dyskinesias (OR 1.68; 95% CI 0.69–4.05; p value 0.2) and wearing-off (OR 0.72; 95% CI 0.31–1.66; p value 0.4), confirmed also at the multivariate analysis, adjusting for sex, LED, age at FU and disease duration at FU (Table 3).

When stratifying the analysis for PD-RBDpre and PD-RBDpost, we found that the presence of hallucinations was significantly associated with PD-RBDpre (OR 4.99; 95% CI 1.44–17.27; p value 0.011) but not with PD-RBDpost (OR 1.50; 95% CI 0.54–4.15; p value 0.4). This association was also confirmed after adjusting for significant confounders (sex, use of dopamine agonists, LED, age at FU and disease duration at FU), with overlapping strength of association for PD-RBDpre (Table 3). There was no association of dyskinesias with either PD-RBDpre (OR 1.25; 95% CI 0.38–4.13; p value 0.7) or PD-RBDpost (OR 1.94; 95% CI 0.74–5.07; p value 0.1). Finally, no association was found with the presence of wearing-off at the FU examination for both PD-RBDpre (OR = 0.37; 95% CI 0.10–1.33; p value 0.1) and PD-RBDpost (OR = 0.96; 95% CI 0.38–2.37; p value 0.9). For both dyskinesias and wearing-off, the results were

confirmed also after adjusting for significant confounders (sex, LED, age at FU and disease duration at FU) as shown in Table 3.

Discussion

In our cohort, we found that almost half of PD patients has a comorbid pRBD, with a higher percentage of patients developing it along the disease course (PD-RBDpost). We also demonstrated that, despite the absence of significant differences at motor onset between PD-RBDpre and PD-RBDpost patients, PD-RBDpre patients are much more likely to be diagnosed with MCI and are at higher risk of developing hallucinations. Overall prevalence of RBD in our sample of PD patients was slightly higher when compared to estimates from a recent meta-analysis [1] albeit in line with other cohorts [2, 17]. When considering the onset of RBD with respect to the motor onset of PD, the prevalence of PD-RBDpre and PD-RBDpost were comparable to studies using only questionnaires or clinical examination to diagnose RBD [11, 18], with a consistent higher representation of PD-RBDpost. Whereas, the estimates in studies using videopolysomnography diagnosis of RBD were either overlapping with our results [10] or showing a higher prevalence of PD-RBDpre [12].

In our sample, PD-RBD+ patients were more frequently diagnosed with MCI when compared to PD-RBD- subjects. The interplay between cognition and RBD has been demonstrated in both patients presenting with idiopathic RBD [19] and patients with PD-RBD, also supported by electroencephalographic (EEG) studies describing similar patterns of overall EEG slowing in both PD-RBD+ [20] and PD-MCI patients [21]. However, when we stratified according to the onset of RBD, a significant difference was present only for the PD-RBDpre subgroup, confirming the previous results of a worse cognitive function in PD-RBDpre patients in a study using PSG confirmed PD-RBD [2]. Other studies investigating the time of onset and the presence of cognitive impairment either found no differences [10, 11] or both PD-RBDpre and PD-RBDpost worse performances compared to PD-RBD- [12]. However, these studies used a general cognitive test, rather than a full neuropsychological assessment and two of them used the MMSE, which has a low sensitivity in the detection of mild cognitive impairment in PD [22]. It is of note that PD-RBDpre compared to PD-RBD- patients displayed higher odds of having an impairment over attention and memory domains, even if the multivariate analysis did not confirm the data regarding the impairment of specific cognitive domains (probably due to the several covariate adjustments and the small sample size). Also, RBD might be associated with sleepiness [23], which in turn can impair cognitive functions and especially attention, representing

Table 3 Hallucinations, dyskinesias and wearing-off at 5 years follow-up

	N (%)	AdjOR	95% CI	p value
Hallucinations*				
PD-RBD- ($n=41$)	11 (26.8)	\	\	\
PD-RBD+ ($n=51$)	21 (41.2)	1.98	0.75–5.24	0.2
PD-RBDpre ($n=16$)	10 (62.5)	4.68	1.24–17.63	0.022
PD-RBDpost ($n=35$)	11 (31.4)	1.25	0.41–3.77	0.7
Dyskinesias**				
PD-RBD- ($n=41$)	11 (26.8)	\	\	\
PD-RBD+ ($n=56$)	21 (37.5)	1.82	0.68–4.86	0.2
PD-RBDpre ($n=19$)	6 (31.5)	2.18	0.57–8.3	0.2
PD-RBDpost ($n=37$)	15 (40.5)	1.66	0.56–4.93	0.3
Wearing-off***				
PD-RBD- ($n=41$)	17 (41.5)	\	\	\
PD-RBD+ ($n=56$)	19 (33.9)	0.64	0.21–1.94	0.4
PD-RBDpre ($n=19$)	4 (21.1)	0.49	0.1–2.36	0.3
PD-RBDpost ($n=37$)	15 (40.5)	0.75	0.21–2.6	0.7

AdjOR: adjusted odds ratios, 95% CI 95% confidence intervals

*Analysis restricted to 92 patients, after removing 5 patients reporting hallucinations at baseline. Models were adjusted considering sex, use of dopamine agonists, LED at FU, age at FU and disease duration at FU

**Models were adjusted considering sex, LED at FU, age at FU and disease duration at FU

a possible confounder. However, no association was found between sleepiness and cognitive impairment in our sample. Literature evidence suggests that the use of clonazepam, as well as the presence of comorbid depression, might increase the odds of cognitive impairment [24, 25]. Nevertheless, we found no association between MCI and clonazepam or depression. Overall, this impairment pattern in PD-RBDpre patients might be the carryover of the cognitive impairment described in iRBD patients at a higher risk of phenoconversion [8] after the appearance of motor symptoms.

In the follow-up assessment, only PD-RBDpre patients had a higher risk of developing hallucinations compared to PD-RBD-. The greater occurrence of hallucinations in PD-RBD+ has been widely described in the literature [3, 12, 26, 27]. However, concerning prospective assessments, few studies have analyzed the risk of developing hallucinations in PD-RBD patients, demonstrating that the presence of RBD increases the risk of future development of hallucinations [28, 29]. Our results, however, suggest that the risk of hallucinations is more strongly related to the occurrence of RBD in the prodromal stage of the disease, rather than after the development of motor symptoms. On the other hand, a cross-sectional study on the association between PD-RBD and hallucinations did not find a differential risk of comorbid hallucinations between PD-RBD patients according to the RBD onset, describing a non-significant higher prevalence of hallucinations in PD-RBDpost patients [18]. However, patients in this latter study had a longer disease duration (8.37 ± 5.35 years), possibly increasing the odds of PD-RBDpost patients to develop hallucinations. PD-RBD and hallucinations have a complex relationship involving altered sleep–wake cycles, cognitive dysfunction and brainstem pathology, all leading to an increased risk of hallucinations [30]. While the presence of an underlying pathology leading to both clinical manifestations is still uncertain, literature evidences suggest that a dysfunction of the pedunculopontine nucleus (PPN), a cholinergic brainstem nucleus, might be one of the substrates of both RBD and hallucinations in PD, as patients with PD and hallucinations have higher PPN atrophy compared to non-hallucinating patients [31] and the PPN has a major role in the regulation of REM sleep [32].

Overall, the results of our study suggest that PD-RBDpre patients, who should represent the “body first” subtype, are a subgroup of PD patients with a more severe disease phenotype, especially considering the cognitive functions. This hypothesis is in line with the evidences of cognitive function in PD mediated by the activity of the brainstem nuclei [33] which could be impaired in the earliest stages of the disease (Stage 2 and 3 of the Braak progression) [34].

Our results should be interpreted with caution due to some limitations. Our sample was relatively small thus reducing the statistical power of some analyses. Moreover,

the retrospective design is associated with a possible recall bias pertaining the exact onset of RBD. Another limitation is related to the absence of polysomnography to determine the presence or absence of RBD, which was based on a questionnaire and thus prone to the inclusion of false positive cases. Also, we could not exclude that some patients had RBD mimics such as Obstructive Sleep Apneas and Restless Leg Syndrome, rather than RBD. However, we used a more stringent cutoff for the RBDSQ score [15] in order to increase the specificity of the questionnaire, giving more cautious estimates. Finally, all enrolled patients were in an early stage of disease, so we cannot exclude that PD patients considered as RBD- may develop RBD later in the disease course.

This study, however, has several strengths. Patients were recruited in the early stages of the disease, reducing the risk of confounding related to advanced age and advanced disease duration on cognitive impairment or hallucinations. Another strength depends on the complete neuropsychological assessment of cognition that allowed for the MCI diagnosis according to modified MDS level II criteria and the evaluation of patients on a longitudinal basis, although with a relatively short follow-up (5 years) from baseline examination.

In conclusion, our results strongly suggest that specific care should be devoted to PD-RBDpre patients in terms of examining cognitive functions and searching for the presence of hallucinations even in the earliest stages of the disease, in order to allow for a better prognostic stratification and a personalized therapeutic approach.

Author contributions CEC: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting of the article; AL: acquisition of data, analysis and interpretation of data, critical review of the article; GM: acquisition of data, analysis and interpretation of data, critical review of the article; GD: acquisition of data, analysis and interpretation of data, critical review of the article; LG: acquisition of data, analysis and interpretation of data, critical review of the article; MZ: analysis and interpretation of data, critical review of the article; AN: conception and design of the study, analysis and interpretation of data, critical review of the article.

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Data availability statement The data supporting the findings of this study are available on request from the corresponding author.

Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards All the patients provided written informed consent to participate in the study. The study has been approved by the Ethical Committee of the AOU Policlinico G. Rodolico-San Marco (111/2019/PO) and has been conducted in accordance to the Declaration of Helsinki.

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