Sleep Medicine 62 (2019) 1–5

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Impaired sleep quality and cognition in patients of Parkinson's disease with REM sleep behavior disorder: a comparative study

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ARTICLE INFO

Article history:
Received 6 October 2018
Received in revised form
15 February 2019
Accepted 1 April 2019
Available online 5 April 2019

Keywords:
Parkinson's disease
Sleep
REM sleep behavior disorder
Neuropsychology
Cognition
Overnight polysomnography

ABSTRACT

Objectives: The present study was undertaken to evaluate the cognitive profile of Parkinson's disease (PD) patients with REM sleep behavior disorder (RBD) and to correlate with the clinical stage and polysomnographic variables.
Methods: The study included 25 PD patients who had RBD and 25 PD patients who based on two questionnaires were determined as not having RBD. These patients underwent overnight polysomnography (PSG) and neuropsychological assessment using a defined battery of tests.
Results: The mean age of the patients with clinically probable RBD (RBD+) was 60.4 ± 8.2 years and PD patients without RBD (RBD-) was 57.3 ± 6.6 years ($p = 0.14$). The mean age at onset of the disease was 53.7 ± 9.4 years for RBD+ and 49.8 ± 7.8 years for RBD-patients ($p = 0.12$). The mean Unified Parkinson Disease Rating Scale (UPDRS) part III OFF score was 27.4 ± 11.1 for RBD+ and 32.7 ± 8.2 for RBD- ($p = 0.06$). The total sleep time of the patients was 4.3 ± 1.7 h with sleep efficiency of 53.8 ± 21.0%. Patients with RBD+ were found to have significant impairment in many neuropsychological tests compared to RBD-.
Conclusions: RBD + patients had significant impairment in MMSE, category fluency test (FAS test), frontal assessment battery, attention (digit span backwards, Corsi span), verbal memory (story recall) and Rey's auditory verbal learning test. These patients also had poor sleep quality.

1. Introduction

Parkinson's disease (PD) is a progressive α-synucleinopathic neurodegenerative disorder characterized by bradykinesia, rigidity, tremors and postural instability [1,2]. In addition to the motor symptoms, these patients frequently have associated non-motor symptoms, some of which can precede the motor symptoms by many years [3]. Furthermore, sleep-wake disturbances are one of the common non-motor symptoms.

REM sleep behavior disorder (RBD) is a parasomnia that occurs during REM (rapid eye movement) sleep and characterized by loss of physiological REM sleep atonia, dream enactment behavior and complex motor behavior or vocalizations [4]. It is predominantly seen in patients with synucleinopathies (eg, multiple system atrophy, dementia with Lewy bodies, PD) with a prevalence of 30–90% [5]. PSG is the gold standard technique to confirm the diagnosis of RBD.

Currently, there are very few studies that have compared the cognitive profile between patients of polysomnography (PSG) confirmed PD with RBD and without RBD. Therefore, the present study was undertaken to evaluate the cognitive profile of these patients and to correlate with the clinical stage and polysomnographic variables.

2. Materials and methods

The present study was conducted in the departments of Neurology and Neuropsychology at the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore. Our study recruited consecutively, PD patients from the Neurology OPD and Movement Disorders Clinic of our institute. The diagnosis

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https://doi.org/10.1016/j.sleep.2019.04.001
1389-9457/

of PD was based on the United Kingdom Parkinson's disease society (UKPDS) brain bank criteria. The presence of RBD was screened for using both the Mayo sleep questionnaire (MSQ) informant version and the RBD sleep questionnaire (RBDSQ) [6,7]. Patients who screened positive on both MSQ and RBDSQ were considered for overnight PSG. Those who screened negative were taken as PD without RBD (RBD-). The study included 31 PD patients who had RBD and 25 PD patients who did not have RBD based on questionnaire. Patients with significant medical comorbidities and other CNS disorders (eg, stroke, other neurodegenerative diseases) which can affect cognition were excluded from the study. Information regarding baseline demographic and clinical data was recorded. Only patients (N = 31) with clinically probable RBD (based on questionnaires) underwent overnight PSG. Sleep was recorded and scored according to the American Academy of Sleep Medicine (ASAM) 2010 criteria. Patients who were on medications that can affect the RBD (eg, clonazepam) stopped use one week prior to PSG. The PSG included placement of the eight channel EEG electrodes according to the 10–20 international system, right and left electro-occulogram and chin EMG activity. All PD patients with and without RBD underwent neuropsychological assessment using a defined battery of tests that included mini mental status examination (MMSE), frontal assessment battery (FAB), Montreal cognitive assessment (MoCA version 7.1), digit span forwards and backwards, verbal fluency test (controlled word association test and animal naming test), Corsi block tapping test, response inhibition (stroop test), Rey's auditory verbal and learning test (AVLT) and a validated story recall test. The details of the methodology is given in Fig. 1.

The study was approved by the Institutional Ethics Committee and all patients were recruited after obtaining an informed written consent.

2.1. Statistical analysis

Statistical analysis was done using R software. Data was expressed using descriptive statistics for continuous variables, mean and standard deviation as well as for categorical variables, frequency and percentage. The data was not normal according to Shapiro Wilk test, therefore non-parametric tests were used. The Mann Whitney U test was used to compare the means of two independent groups. Additionally, a p value of <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

Thirty-one PD patients with clinically probable RBD (RBD+) based on the MSQ and RBDSQ as well as 25 PD patients without RBD (RBD-) were included in the study. Furthermore, 74.1% of the patients had onset of RBD after the onset of PD. Of the 31 patients, 25 had PSG confirmation of RBD and were included for further analysis. The mean age of RBD + patients was 60.4 ± 8.2 years and RBD-patients was 57.3 ± 6.6 years ($p = 0.14$). The mean age at onset of the disease was 53.7 ± 9.4 years for RBD+ and 49.8 ± 7.8 years for RBD-patients ($p = 0.12$). The mean duration of illness was 6.8 ± 4.6 years for RBD+ and 7.5 ± 3.5 years for RBD- ($p = 0.54$). The mean

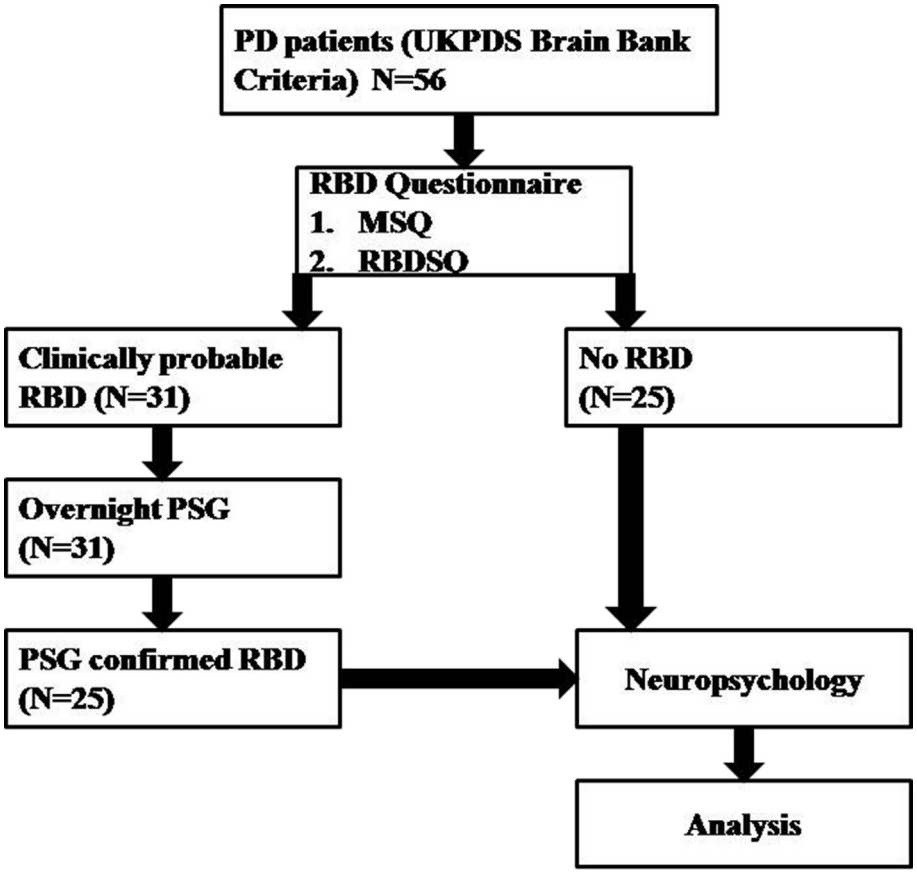

Fig. 1. Study design. MSQ: Mayo sleep questionnaire, PSG: Polysomnography, RBD: REM sleep behavior disorder, RBDSQ: RBD sleep questionnaire.

UPDRS part III OFF score was 27.4 ± 11.1 for RBD+ and 32.7 ± 8.2 for RBD- (p = 0.06). The total levodopa equivalent daily dose was 754.8 ± 349.7 mg/day for RBD+ and 535.8 ± 178.9 mg/day for RBD- patients. The mean MSQ score was 5.3 ± 1.2 for RBD- and for RBD+6.8 ± 1.1 and the mean RBDSQ score was 7.5 ± 1.0 for RBD- and for RBD+ was 8.9 ± 1.0. RBD preceded the motor symptoms of PD in 18.5% and in 74.1% it developed after the onset of motor symptoms of PD. Comparison between the two groups is given in Table 1.

3.2. Overnight polysomnography results

The PSG findings are summarized in Table 2. Overall, 25 patients were found to have RBD after PSG confirmation. RBD confirmation was based on visual determination for REM sleep without atonia (RSWA) and video recording of the RBD behavior. Among the 25 patients who had RBD confirmation on PSG, 17 (68%) patients demonstrated RBD during the later phase of the sleep. Majority of the RBD events occurred after 3:00 am (58.8%). Furthermore, the frequency of RBD increased beyond 3:00 am.

3.3. Neuropsychological results

Patients with RBD+ were found to have significant impairment in many neuropsychological tests compared to RBD-. They had significant impairment in MMSE, category fluency test (FAS test), frontal assessment battery, attention (digit span backwards, Corsi span), verbal memory (story recall), and the Rey's auditory verbal learning test. There was no significant difference found for MoCA, animal naming test, digit span forwards and response inhibition (stroop test). Comparison between the two groups is shown in Table 3.

3.4. Correlation of the clinical variables with the neuropsychological and polysomnographic scores

Most of the neuropsychological tests had negative correlation with the duration of illness, UPDRS, MSQ and RBDSQ of which only MMSE significantly correlated with duration of illness (p = 0.02) (r = −0.03) and UPDRS part III (p = 0.03) (r = −0.4). There was no correlation between the clinical variables and PSG parameters.

4. Discussion

RBD is a forerunner of many neurodegenerative disorders mostly of alpha-synucleinopathy type [8]. In humans it has been shown that locus ceruleous, pontine and midbrain tegmentum are involved in the generation of RBD [9]. It has been postulated that in patients of PD the earliest change occurs in the medulla or pontine tegmentum and olfactory bulb [10]. The pathological process spreads in a rostral direction ultimately involving the cortex.

RBD usually precedes PD as the pathology starts in the brainstem and then ascends upwards [11,12]. This was demonstrated by Braak [10].

Brainstem nuclei such as locus coeruleus, pontine tegmentum and ventral medulla are involved in RBD and its generation is thought to be due to bypassing of the extrapyramidal system [13–15].

There are several differences between PD patients with and without RBD. In a small series, RBD more frequently affected patients with predominant akinetic-rigid rather than the tremor form of PD [16]. In a cross-sectional series, RBD was associated with older age, longer disease duration, higher Hoehn & Yahr stages and reduced response to medication, more falls, motor fluctuations, psychosis and requiring a higher dose of levodopa [12,17,18].

In our study, there were much inter-individual variations in sleep efficiency, the percentage of REM sleep, and total number of RBD patients. In studies where consecutive two days PSG was done, there was intra-individual variations as well [17]. This is due to the first night effect. Performing a PSG on the second day helps to better characterize the sleep.

Numerous studies have used the neuropsychological battery in the attention/executive, memory, language, and visuospatial domains [19]. Furthermore, these studies have found lower performance on neuropsychological tests measuring attention, executive functions and learning [19]. Similar deficits in above domains on neuropsychological assessments have been found in synucleinopathies by various authors. Patients with longer duration of illness and higher UPDRS score have more and rapid decline of cognition [20,21].

Impairment of cognition as measured by the neuropsychological tests predicts future development of dementia [22,23].

The specific physiological, biochemical and anatomical changes that underlie the development of cognitive impairment in PD with RBD are not well-understood [24]. It appears that the cognitive decline is attributable to the loss of cholinergic neurons from the basal nucleus of Meynert (which provides diffuse cortical cholinergic inputs) or is due to brainstem changes. Involvement of cholinergic ponto– geniculo– occipital circuits, which are activated in REM sleep, has been hypothesized in the pathophysiology of hallucinations. Recent reports of beneficial effects of cholinesterase inhibitors, both on hallucinations and on cognitive impairment in PD, also support the hypothesis of cholinergic system involvement [25]. Moreover, the few case reports of positive effects of cholinesterase inhibitors also on RBD further suggest a common neurobiological substrate of these three symptoms [26]. This theory is supported by another study whose objective was to assess the cholinergic function, as measured by short latency afferent inhibition (SAI) in PD with RBD patients using transcranial magnetic

Table 1
Characteristics of the patients.

Characteristics	PD without RBD	PD with RBD	p-Value
Total no. of patients	25	25	–
Age (years)	57.3 ± 6.6	60.4 ± 8.2	0.14
Age at Onset (years) (mean ± SD)	49.8 ± 7.8	53.7 ± 9.4	0.12
Duration of illness (years) (mean ± SD)	7.5 ± 3.5	6.8 ± 4.6	0.54
UPDRS part III (OFF state) (mean ± SD)	32.7 ± 8.2	27.4 ± 11.1	0.06
Duration of RBD (years) (mean ± SD)	–	2.8 ± 2.6	–
T-LEDD (mg/day)	754.8 ± 349.7	535 ± 178.9	<0.001
MSQ (mean ± SD)	5.3 ± 1.2	6.8 ± 1.1	0.08
RBDSQ score (mean ± SD)	7.5 ± 1.0	8.9 ± 1.0	0.04

RBDSQ: REM sleep behavior disorder sleep questionnaire, MSQ: Mayo sleep questionnaire, T-LEDD: Total levodopa equivalent daily dose, UPDRS: Unified Parkinson's Disease Rating Scale.

Table 2
Polysomnographic characteristics of patients with PD and RBD.

Parameter	Value (Mean ± SD)
Total sleep time (TST) (hours)	4.3 ± 1.7
Sleep efficiency (%)	53.8 ± 21.0
Sleep latency (min.)	26.6 ± 25.0
Stage R latency (min.)	158.1 ± 135.6
Stage N1 duration (min.)	72.3 ± 46.6
Stage N2 duration (min.)	106.9 ± 71.5
Stage N3duration (min.)	21.6 ± 25.6
Stage R duration (min.)	59.4 ± 18.7
No. of Arousals (Mean ± SD)	91.9 ± 72.8
Arousal Index	20.7 ± 4.4
Apnea-Hypopnea Index (AHI)	4.9 ± 11.2
No. of Obstructive apneas (Mean ± SD)	4.5 ± 7.6
No. of Central apneas (Mean ± SD)	0.9 ± 0.7
No. of Mixed apneas (Mean ± SD)	0.4 ± 1.7
Min. O_2 Saturation (Mean ± SD)	85.3 ± 9.8
Max. O_2 Saturation (Mean ± SD)	99.8 ± 0.4
No. of Desaturations (Mean ± SD)	10.9 ± 14.2
Desaturation Index	5.6 ± 17.0
Average Heart Rate/min	68.7 ± 9.0
No. of PLMs (Mean ± SD)	36.5 ± 29.6
PLMI	10.3 ± 5.8
No. of RBD episodes[a] (Mean ± SD)	10.1 ± 4.2

PLMS: Periodic limb movements, PLMI: Periodic limb movement index.
[a] RBD episodes include both RBD behavior and REM sleep without atonia (RSWA).

Table 3
Neuropsychological profile of patients.

Neuropsychology Test	PD without RBD	PD with RBD	p-Value
MMSE	28.6 ± 1.2	27.6 ± 1.9	0.03
MoCA	27.0 ± 1.2	26.8 ± 2.4	0.71
Animal naming test	12.0 ± 4.4	10.6 ± 1.9	-<0.001
FAS test	21.8 ± 6.6	11.8 ± 2.1	<0.001
FAB score	16.6 ± 0.7	14.7 ± 3.0	0.004
Digit span forwards	4.9 ± 0.8	5.2 ± 0.7	0.89
Digit span backwards	3.9 ± 0.7	3.4 ± 0.6	<0.001
Story recall (Immediate)	11.2 ± 2.8	8.6 ± 2.5	0.001
Story recall (Delayed)	9.2 ± 1.9	7.2 ± 2.6	0.002
Stroop effect	147.4 ± 39.5	150.5 ± 63.6	0.88
Corsi span	5.2 ± 0.7	4.6 ± 0.6	0.001
AVLT 1	7.1 ± 2.2	4.8 ± 0.9	<0.001
AVLT 2	8.8 ± 2.2	5.9 ± 1.5	<0.001
AVLT 3	9.9 ± 2.5	6.8 ± 1.6	<0.001
AVLT 4	11.6 ± 2.2	7.7 ± 2.1	<0.001
AVLT 5	12.6 ± 2.5	8.6 ± 1.9	<0.001
IR	11.2 ± 2.5	7.2 ± 1.7	<0.001
DR	9.8 ± 2.0	6.6 ± 2.1	<0.001

AVLT: Auditory verbal learning test, DR: delayed recall, FAB: frontal assessment battery, IR: immediate recall, MMSE: mini mental status examination, MoCA: Montreal cognitive assessment.

stimulation measured SAI and tried to correlate with a comprehensive battery of neuropsychological tests [27]. Mean SAI was significantly reduced in PD-RBD patients. SAI values correlated positively with neuropsychological tests measuring episodic verbal memory, executive functions, visuo-constructional and visuo-perceptual abilities. SAI abnormalities suggest a cholinergic dysfunction in PD patients who develop cognitive impairment, and indicate that RBD is an important determinant of MCI in PD.

Thus, in patients with RBD there is an imbalance between the various neurotransmitter systems, making these patients a unique entity with a propensity to develop significant cognitive impairment. It appears that presence of RBD is an independent risk factor for cognitive impairment.

Our study had several limitations. These include a small sample size, element of selection bias, lack of RSWA analysis and not including the non-RBD patients for PSG.

5. Conclusions

Patients of PD with RBD have significant impairment of sleep and cognition. Moreover, overnight PSG is an important tool to investigate the sleep disturbances in patients of PD with RBD. Finally, these patients needs to be identified and considered as a distinct type of PD that requires additional care since these patients are more prone for psychosis, less responsive to medications, more frequent motor fluctuations, frequent falls and early and severe cognitive impairment.

Source of funding

This research received partial grant from Indian council of medical research (ICMR). Grant no. ICMR/003/304/2013/00694.

Conflict of interest

The authors have no conflict of interest to report.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.04.001.

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