

Clinical Correlates of RBD in Early Parkinson Disease

Astrid Haram^{1,2*}, Erik Hessen^{3,4}, Eirik Auning^{1,6}, Ane Lovli Stav³, Bradley Boeve⁵, Carl Fredrik Eliassen^{3,4}, Eyvind Rugland³, Abdolreza Esnaashari³, Tormod Fladby^{1,3} and Dag Aarsland^{7,8}

¹Institute of Clinical Medicine, Campus Ahus, University of Oslo, Norway

²Ostfold Central Hospital, Department of Geriatric Psychiatry, Fredrikstad, Norway

³Akershus University Hospital, Department of Neurology, Lorenskog, Norway

⁴Department of Psychology, University of Oslo, Norway

⁵Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA

⁶Akershus University Hospital, Department of Geriatric Psychiatry, Lørenskog, Norway

⁷Alzheimer's Disease Research Centre, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Novum, 141 86 Stockholm, Sweden

⁸Centre for Age-Related Diseases, Stavanger University Hospital, 4000 Stavanger, Norway

*Corresponding author: Astrid Haram, Ostfold Central Hospital, Department of Geriatric Psychiatry, (Alderspsykiatrisk seksjon), 1603 Fredrikstad, Tel: +47 93026972; E-mail: astrid.haram@gmail.com

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Abstract

Objective: Knowledge of the cognitive performance associated with REM sleep behavior disorder (RBD) in newly diagnosed Parkinson disease (PD) patients is limited. We thus wanted to explore 1) the frequency of RBD in patients with PD at a relatively early stage and 2) cognitive performance associated with RBD in PD. We hypothesized that RBD would be associated with cognitive impairment in PD.

Methods: 29 non-demented patients recently diagnosed with PD (disease duration <5 years, Hoehn and Yahr stage <2.5 and no dementia) were recruited. The diagnosis of PD was supported by dopamine transporter SPECT. RBD was diagnosed based on standardized clinical interview and confirmed by polysomnography. Overall cognition was assessed by screening tests including the Mini-Mental State Examination (MMSE), and neuropsychological tests of memory, language, executive, attentional and visuospatial functions tests were performed.

Results: 13 patients (45%) had probable RBD. There were no significant differences between PD with and without RBD in any of the neuropsychological tests, but a numerically lower performance was observed in the PD RBD group on memory tests

Conclusions: RBD is common even in early PD without dementia, but was not found to be associated significantly with cognition.

Keywords: Parkinson disease; Rem sleep behavior disorder; Neuropsychology; Cognition

Introduction

REM sleep behavior disorder (RBD) is a distinct parasomnia characterized by both abnormal REM sleep electrophysiology (i.e., REM sleep without atonia or RSWA) and abnormal REM -sleep behavior. Clinical features include abnormal vocalizations, abnormal motor behavior and altered dream mentation.

RBD is associated with cognitive impairment. In a population based study Boot et al. [1] followed 651 cognitively intact participants, including 44 patients with baseline pRBD. After four years, 32% of RBD patients were classified as mild cognitive impairment (MCI), an intermediate state between intact cognition and dementia, compared to 15% in those without RBD. In another study 16 of 32 RBD patients referred to a sleep center met criteria for MCI [2]. MCI has also been observed in PD [3,4], and 20-25% of PD patients without dementia have MCI [5]. Of note PD-MCI has shown to be a prodromal phase of dementia in PD (PDD) [6,7].

Few studies have studied the cognitive correlates of RBD in patients with PD. Our objective was to explore 1) The frequency of RBD in PD patients at a relatively early stage, and 2) cognitive performance and other clinical features associated with RBD in PD. We hypothesized that RBD would be associated with cognitive impairment in PD, including more common in those with MCI.

Methods

Subjects

Patients with PD were consecutively recruited from a university-hospital based neurological outpatient clinic during 2011- 2013. Inclusion criteria were diagnosis of PD [8], disease duration less than 5 years, and a bed-partner. A pathological single photon emission computed tomography (SPECT) using an ioflupane (¹²³I) biomarker (DaT SCAN) was required to support the diagnosis of PD. Exclusion criteria were dementia (see below), somatic (other than PD), psychiatric or other disease that might have contributed to cognitive

impairment (including drug abuse, major depression, solvent exposure, anoxic brain damage) and active cancer.

Clinical Assessment

All PD patients were examined by a neurologist with training in movement disorders who made the diagnosis of probable PD [8] based on the presence of 3 out of 4 features: asymmetric onset, bradykinesia, rigidity and resting tremor. The only exception from the criteria was that the requirement of disease duration more than 3 years was not met by 13 patients (Table 1).

Variables	PD with pRBD (n=13)	PD confirmed with RBD on PSG (n=7)	PD non-RBD (n=16)
Age, years	65.5	64	64.6
Females, n (%)	5 (38.5)	3 (42.9)	7 (43.8)
Disease duration, years	2.2 (1-5)	2.2 (1-5)	2.9 (0.5-6)
MMSE score	28.9 (26-30)	29 (26-30)	29 (26-30)
UPDRS part III motor subscale score	11.8 (6-26)	10.1 (6-17)	14.7 (3-31)
Hoehn and Yahr stage (1/1.5/2/2.5), n	5/4/3/1	2/2/2/1	5/3/4/4
GDS stage 1/2/3, n	7/3/2003	3/1/2003	8/3/2005
MCI n %	3 (23.1)	3(42.9)	5(31.3)
Education, years	12.3 (7-18)	11.7 (6-17)	12.7 (8-19)
NMSS	9.7 (4-7)	10.4 (6-17)	7.1(4-18)
Geriatric depression scale	1.6 (0-4)	1.1 (0-3)	1.1 (0-3)
L Dopa Equivalent Dosage	287.5 (100-662)	369.6 (100-662)	403 (100-662)

Table 1: Baseline characteristics, Numbers represent mean (range) or number of patients (%), *p<05 (pRBD vs non-RBD), t-test, PSG: Polysomnography, MMSE: Mini-mental state examination, GDS: Global deterioration scale 1 (normal), 2 (Subjective cognitive impairment) and 3 (mild cognitive impairment), NMSS: Non-motor symptom scale. Standardized rating scales of motor function [9] (UPDRS part III, motor sub-scale) and Hoehn and Yahr staging [10] were performed by trained research physicians. Drug use was recorded, and L-DOPA equivalents calculated [11].

Depression was assessed using the 15-item Geriatric Depression Scale [12].

The Non-motor symptom scale (NMSS) [13] was completed.

Cognitive assessment and classification

All subjects completed assessment of cognitive function, consisting of a clinical interview of the patient and the bed-partner, MMSE and several domain-specific cognitive screening tests [14]. Based on this assessment, cognitive staging was decided by consensus according to the Global Deterioration Scale (GDS) [15] defined as: 1= normal cognition, 2= subjective cognitive impairment, 3= MCI as previously

described [16]. Subjects with GDS score 4 or higher (i.e dementia), were excluded.

In addition, tests of memory, executive functioning and visuospatial ability were administered by a neuropsychologist [17]. One patient did not show up for the neuropsychological evaluation. Episodic verbal memory was assessed by the Rey Auditory Verbal Learning Test-Delayed Recall (RAVLT-DR) [18] and by Logical Memory – Delayed Recall [19] Visuospatial ability was assessed by the Rey Complex Figure Test (RCFT) [20,21]. Aspects of executive functions were assessed by tests measuring divided attention, (Trail Making Test-B (TMT-B) [22], response inhibition (Stroop) [23] and word fluency (FAS) [24,25].

Diagnosis of REM - sleep behavior disorder

Clinical features of RBD were elicited using Mayo Sleep Questionnaire (MSQ) [25] Answering “yes” on the question “Has the patient appeared to “act out his/her dreams” while sleeping? (Punched or flailed arms in the air, shouted or screamed) was accepted as probable RBD (pRBD). Both the patients and spouses were answering the MSQ. Informants answered “yes” only if dream enactment behavior occurred at the least three times. The MSQ has been validated and found to have a sensitivity of 98% and specificity of 74% for the diagnosis of RBD [26]. Patients with affirmative answers on the MSQ were referred to polysomnography (PSG), and RBD was diagnosed according to American Academy of Sleep Medicine (AASM) – criteria [27].

Polysomnography

All sleep recordings were made with titanium ambulatory sleep recording equipment. The patient was fitted with electrodes and sensors and was monitored with electroencephalography, electro-oculography, and surface submental and the tibialis anterior electromyography. Respiration was recorded with a nasal pressure gauge. O2 saturation was monitored on the index finger. Thorax and abdominal circumference was measured with registration belts and a snore sensor and position sensor was also used. AASM guidelines for layout of electrodes and sensors were followed [28].

The records were read and interpreted in the Somnologia sleep interpretation application. Scoring of sleep stages, arousals sleep latency time and sleep efficiency was performed. The EMG tone was rated during REM sleep. Periodic limb movement (PLM) activity was scored and rated. Obstructive, mixed and central apnoeas and hypopneas were scored and the apnea/hypopnea index (AHI) was calculated. Episodes of brief interruptions of breathing (apnea) or significantly reduced respiration (hypopnea) were counted when lasting more than ten seconds. The AHI is calculated by dividing the number of events by the number of hours of sleep (AHI values are typically categorized as 5–15/hr = mild; 15–30/hr = moderate; and > 30/h = severe). Lowest O2 saturation, degree of snoring and time in the supine position was also assessed. The parameters were scored and evaluated according to AASM guidelines [29]

Assessments were compiled in a report which concludes whether or not the patient meets the criteria for RBD. It was also assessed whether the patient had sleep apnea syndrome and /or PLM and their extent. This was done blind to the cognitive assessments. Patients were classified as definite RBD (clinical and PSG confirmed), pRBD (clinical confirmed according to MSQ) and no RBD [27].

Statistics

SPSS/PASW statistic version 20 was used for statistical analyses and $p < 0.05$ was considered statistically significant. Descriptive statistics of the demographics were computed. The demographic characteristics including age, education and MMSE were similar between the two groups, thus raw scores of the neuropsychological tests were used and independent t-tests were performed to compare neuropsychological function (after confirming the normal distribution of data) between the PD patients with and without RBD.

Ethical considerations

The study protocol was approved by the South-Eastern Norway ethical committee for medical research and written informed consent was obtained from all subjects before any study-specific procedures were performed.

Results

29 patients were included in the project, and their characteristics are shown in Table 1. PD patients with and without RBD did not differ significantly for age, level of education and MMSE. At inclusion, 27 patients used levodopa, 15 used both dopamine agonists and levodopa, 12 only dopamine agonists and 2 patients used no dopaminergic medication [11]. Two patients used citalopram antidepressants but no patients used benzodiazepines, melatonin, antipsychotics, acetylcholinesterase inhibitors or agents to treat RBD.

According to Mayo Sleep Questionnaire 13 patients (45%, 38.5% of them female) had pRBD, and 16 had no RBD. Among 11 of 13 patients with pRBD who completed PSG (two patients refused), 7 had a typical RBD pattern on PSG, whereas in four patients RBD could not be confirmed. Two of these patients had insufficient REM sleep to be certain, and the other two patients had normal EMG atonia during REM sleep. In addition, 4 patients had PLM, all with confirmed RBD, and two had obstructive sleep apnea.

Cognition and other clinical correlates of RBD in PD

There were no significant differences between PD with and without pRBD in any of the neuropsychological tests. However, we found numerically lower performance in the PD RBD group on the Logical Memory test (WMS-R) ($p=0.09$) (Table 2), with a relatively high effect size of 0.68. Similarly, depression and motor scores did not differ. However, the NMSS was higher in the pRBD compared to the non-RBD group ($p < .05$). Among the five items with the largest difference between the two groups, two were related to RBD 24 (intense, vivid dreams or frightening dreams, and item 25: talking or moving about in your sleep as if acting out a dream), in addition to item 13 (loss of interest in what is happening around you or doing things, item 11 (unexplained change in weight), and item 1 (dribbling of saliva during daytime).

Neuropsychological test results – Raw scores	Non-RBD group (n=15)	pRBD group (n=13)
RAVLT-delayed recall	8.6 (3.4)	7.3 (3.2)
Logical memory 2 – delayed recall	23.8 (6.3)	19.1 (7.8)A
RRCFT 30 – delayed recall	14.2 (7.0)	14.2 (6.9)
TMT-B	163.5 (104.4)	148.9 (94.3)

COWAT	32.9 (13.5)	38.5 (8.4)
Stroop Color-Word	73.1 (26.1)	70.5 (17.5)

Table 2: Neuropsychological test results. Scores in PD patients with and without RBD.

Numbers represent mean (SD) scores. A=0.09, RAVLT: Rey Auditory Verbal Learning Test, Logical memory 2: Wechsler Memory Scale subtest logical memory, RCFT 30: Rey-Osterrieth complex Figure test delayed recall 30 min, TMT-B: Trail Making Test part B, COWAT: Controlled Oral Word Association Test

Discussion

The main finding of this study was that 45% of patients with PD at mild to moderate stage and without dementia had probable RBD. Contrary to our hypothesis, there were no significant differences in cognitive performance between those with and without RBD, and no significant association between MCI and RBD. However, the RBD group scored poorer on verbal memory with a relatively large effect size. The NMSS was increased in those with RBD, which was mainly driven by RBD-related items.

Our finding that nearly half of this cohort with mild-to-moderate severe PD had RBD is consistent with previous studies, which have found the proportion of RBD in PD to vary between 46% - 58% using different methods and criteria to define RBD [30-32].

Several previous studies have reported RBD in PD to be associated with cognitive impairment and other typical features associated with Lewy-body disease including depression, orthostatic hypotension, and other sleep problems, even in de-novo PD [33]. Of interest, prospective studies have found that RBD is a risk factor for subsequent development of dementia and hallucinations in PD [34-36], suggesting that RBD is a marker or risk factor for more wide-spread cortical pathology in PD.

RBD reflects pathology in the brainstem circuitry involved in REM sleep control, and while the pathophysiology of human RBD remains unclear, degeneration of the subceruleus region (such as the sublaterodorsal nucleus) and/or magnocellular reticular formation has been hypothesized. For unclear reasons, involvement of these structures combined with the PD-related pathology of substantia nigra, seem to precede the evolution of α -synuclein deposition and the associated neurodegenerative changes in limbic structures and neocortex following the Braak staging system (Braak, 2003; Braak, 2004). This evolution in the topography of pathology could explain why RBD tends to precede the onset of the typical cognitive and neuropsychiatric manifestations of PD. However, relatively few studies have explored the underlying mechanisms of the association between RBD and cognitive impairment. Murray et al. [37] aimed to determine structural MRI and digital microscopic characteristics of RBD in individuals with dementia with Lewy bodies at autopsy, and found that pRBD is associated with a higher likelihood of Lewy body pathology and less severe Alzheimer-related pathology in the medial temporal lobes, whereas absence of pRBD is characterized by Alzheimer-like atrophy pattern and increased phospho-tau burden.

Limitations of our study include the small sample size, and thus the statistical power is reduced and the observed lack of association between RBD and cognition should be interpreted with caution. Another limitation is the cross-sectional design, and it is possible that longitudinal follow-up would have identified an association between

RBD and cognitive impairment. Finally, PSG was not available for all patients, and thus the diagnosis of RBD cannot be ascertained in all cases. However, previous studies have found that most patients with probable RBD have the diagnosis confirmed with PSG [26], and this was also supported by our findings. Strengths of the study include the homogenous cohort with respect to disease duration and stage, and well-characterized patient group, the use of standardized tests for cognitive and RBD assessment, the identification of PD with MCI, and the use of PSG and DAT scan to ascertain the RBD and PD diagnoses.

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