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ORIGINAL COMMUNICATION

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Is REM sleep Behaviour Disorder (RBD) a risk factor of dementia in idiopathic Parkinson's disease?

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Abstract *Objective* To study the sequence of occurrence of REM-sleep behaviour disorder (RBD) and dementia and their frequency among a population of patients with idiopathic Parkinson's disease (PD). *Methods* We performed a cross-sectional study on 65 PD patients seen in a movement disorder clinic and their bed partner, and asked them to complete the validated Mayo Sleep Questionnaire for RBD and sleep disorders. The diagnosis of PD with dementia (PD-D) was based on a clinical diagnosis of dementia; following DSM-IV criteria and MMSE score less than 25 and a battery of cognitive tests. *Results* From the 65 patients that completed the study, twenty-four met the clinical diagnosis of RBD. Ten of the 24 (42%) RBD patients met the clinical criteria of PD-D, whereas the remaining 14 patients were non-demented at the time of the study. The frequency of RBD was significantly higher in the PD-D group (n=10, 77%) compared to the PD-ND group (n=14, 27%, chi squared test: p=0.0008). PD non-RBD had a lower occurrence of dementia (7.3%, 3 of 41) compared to those suffering from RBD (42%, 10 of 24). Of the 65 PD patients, 13 were diagnosed with PD-D and the remaining 52 were non-demented PD (PD-ND) patients. PD with RBD showed a faster decline in the number of dementia-free patients compared to the non-RBD patients (Log Rank test: p<0.001). RBD preceded, coincided or followed the onset of the motor symptoms. *Conclusion* This study shows that RBD and dementia have a significant coincidence in the course of PD, and RBD not only precedes or coincides with the motor signs, but can occur during the course of the progression of the PD, suggesting a degenerative process of the dopaminergic and cholinergic neurons of the brainstem nuclei, progressing at a different pace in each patient.

Key words Parkinson's disease · dementia · risk factors · REM sleep behaviour disorder (RBD)

Introduction

REM sleep behaviour disorder (RBD) is a distinct clinical condition that was first described by Schenck in 1986 [26] and is characterised by vivid dreams, often frightening, associated with simple or complex motor behaviour during REM sleep. Patients with RBD can always recall the dream if woken up during the episode [25]. RBD has been implicated as a heralding feature of neurodegenerative disorders [6], and 38% of idiopathic RBD patients were shown to develop a parkinsonian disorder at a mean of 3.7 years after the diagnosis of RBD. One-third of Parkinson's disease (PD) patients have been reported

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to have RBD based on polysomnography (PSG) diagnosis. Previous studies have shown that RBD can be an early feature of alpha synucleinopathy with RBD occurring in 47% of IPD and 80% of Lewy body dementia (DLB), compared to only 2% in Alzheimer's dementia [5, 6] with the onset of RBD preceding or coinciding with the onset of dementia or parkinsonism.

A neuropathological study by Braak et al. [11] proposed the existence of an ascending neurodegenerative process in PD pathology, as a possible explanation for the sequential involvement of brain regions in PD. We studied the time of onset of RBD and dementia and their frequency among an idiopathic PD (PD) population, to test the hypothesis that RBD could be a predictor of dementia in PD.

Methods

Subjects

We performed a cross-sectional study on 65 patients with PD (41 men and 24 women; mean age ± SD, 68.06 ± 11.18 years; mean duration of disease ± SD, 7.44 ± 6.64), seen in the movement disorder clinic at St. George's Hospital, London. Patients were included in the study if they were clinically diagnosed with PD according to the clinical diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank [21]. The diagnosis of PD with dementia (PD-D) was made on the combination of the clinical diagnosis of dementia due to PD, based on the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, code 294.1) criteria and MMSE score of less than 25. The onset of the cognitive changes had to be at least one year after the onset of parkinsonism features, in order to clinically exclude DLB patients [23]. Other parkinsonian syndromes were excluded. The date of onset of motor symptoms, dementia and RBD were recorded from case notes, including regular MMSE scores performed in the movement disorders clinics, and also from partner and patient interview. Patients and their bed partner were provided with information sheets on the study and a written informed consent was obtained from the patient or the legally authorised partner.

Clinical interview

A clinical interview was conducted with the patient and their partner, in which a diagnosis of dementia was confirmed or excluded according to the DSM IV criteria. The patient was diagnosed with dementia if the patient or the informant reported impairment in social or occupational functioning along with memory decline and downgraded ability to manage complex tasks (executive function) such as, for example, electronic equipment in the home. A history from the informant was taken for daytime and nocturnal hallucinations, the patient and their bed partner were asked to complete the validated Mayo Sleep Questionnaire (MSQ) [7, 8] to determine the presence of RBD, along with a history of limb or body movement during sleep observed by the bed partner. RBD was diagnosed according to previous published criteria defined in 1997 by the International Classification of Sleep Disorders [3] that includes movement of limbs or body associated with dream mentation, and at least one of the following: potentially harmful sleep behaviours, dreams that appear to be acted out, or sleep behaviours that disrupt sleep continuity. The MSQ also looked for the presence of Restless Legs syndrome (RLS) and daytime sleepiness (Epworth Sleepiness Scale). The investigations also included completion of the Mini Mental State Examination (MMSE) and the Hoehn and Yahr staging scale.

Cognitive tests

The investigation was completed with a battery of tests. Verbal production ability was tested by the initial letter verbal fluency test. Visual spatial tests included shape detection, fragmented numbers and scattered dot counting from the cortical vision-screening test. Concentration and organisational skills (executive function) were assessed with the clock drawing test and the Symbol Digit Modalities test. Visuo-constructional ability was assessed with copying of the Rey-Osterrieth Complex Figure. The tests were administered and scored according to published criteria [13, 28, 32].

Statistical analysis

The data was analysed using SPSS version 11 for Windows. Means and standard deviations were determined for the data. The distribution of RBD in PD and PD-D were analysed using the chi-squared test. The normality of the distribution was assessed by the skewness of the values. In case of non-normally distributed data nonparametric analysis (Mann-Whitney U test) was used otherwise the student T test was applied. From the outcome a two-tailed p value was obtained and the threshold of significance was considered 0.05.

The risk of dementia in the two groups; RBD and non-RBD was determined by the survival curve analysis, which was achieved by using the SAS software. For the significance testing of the risk of dementia in RBD and non-RBD the Log Rank test was applied.

Results

Frequency of RBD and dementia in the PD population

From the 65 patients who completed the study, twenty-four (37%; 17 men and 7 women; mean age of PD patients = 67.54 ± 6.66 years; mean duration of disease ± SD = 7.04 ± 5.95 years: mean Hoehn and Yahr stage ± SD = 3 ± 1.02) met the clinical diagnosis of RBD. The age of onset and the duration of Parkinson's disease were not different between the RBD (mean age at onset = 60.21 years, duration = 7.04 years) and the non-RBD group (mean age at onset = 60.73 years, duration = 7.67 years). Four RBD and 8 non-RBD patients presented with a family history of Parkinson's disease.

Of the 65 PD patients, 13 (25%) were diagnosed with PD-D and the remaining 52 were PD-ND patients. The mean age of onset was not different between PD-D (59.3 years) and PD-ND group (60 years), but the duration was longer in the PD-D (11.15 years) compared to the PD-ND group (8.2 years, $p < 0.05$).

Frequency of RBD versus dementia

Ten of the 24 (42%) RBD patients met the clinical criteria of PD-D, whereas the remaining 14 patients were non-demented at the time of the study, but had a shorter duration of Parkinson's disease (mean ± SD = 5 ± 4.15 years) compared to demented RBD patients (mean ± SD = 9.9 ± 7.06 years). The frequency of RBD

Table 1 Number and percentage of patients suffering from REM sleep Behaviour Disorder (RBD) in the PD-Non Demented (PD-ND) and PD-Demented (PD-D) groups

	PD	PD-ND	PD-D
RBD	n = 14	n = 10	n = 24
Non-RBD	n = 38	n = 3	n = 41
Total	n = 52	n = 13	n = 65

(Table 1) was significantly higher in the PD-D group (n = 10, 77 %) compared to the PD-ND group (n = 14, 27 %, chi squared test: p = 0.0008). PD non-RBD had a lower occurrence of dementia (7.3 %, 3 of 41) compared to those suffering from RBD (42 %, 10 of 24). PD with RBD showed a faster decline in the number of dementia-free patients compared to the non-RBD patients (see Fig. 1) (Log Rank test: p < 0.001).

In the RBD group 10/24 patients reached the clinical state of dementia with a median duration of 8.5 years (range: 1–18 years) from the onset of PD, whereas 3/41 non-RBD patients reached dementia with a median duration of 12 years (range: 2–23 years) from the onset of PD motor symptoms.

Time course of RBD

In the PD-ND group, RBD preceded the motor symptoms in 4 cases (median interval = 4.5 years, range 2–38 years) and coincided with the onset of the motor symptoms in 3 other cases. However RBD followed the onset of the motor symptoms in 7 patients (mean interval: 5 years, range: 1–10 years).

In the PD-D group, all the 10 cases of RBD came after the motor signs. Seven patients developed dementia after the onset of RBD with a median of 4 years (range = 0.5–12 years), and 3 developed dementia before the onset of RBD with a median of 1 year (range = 0.5–1 year).

Other sleep disorders

PD-RBD had a higher occurrence of night hallucinations (9/24; 37.5 %) than those in PD non-RBD (2/41; 4.9 %; p = 0.001). The frequency of RLS was significantly higher in the RBD (9/24; 37.5 %) compared to the non-RBD group (7/41; 17.07 %: p < 0.05). The mean score of Epworth Sleepiness Scale was 10.25 in the RBD group and 8.37 in non-RBD patients (p > 0.05).

Cognitive functions

PD with RBD had a tendency to score lower in the verbal fluency test and the symbol digit modalities test

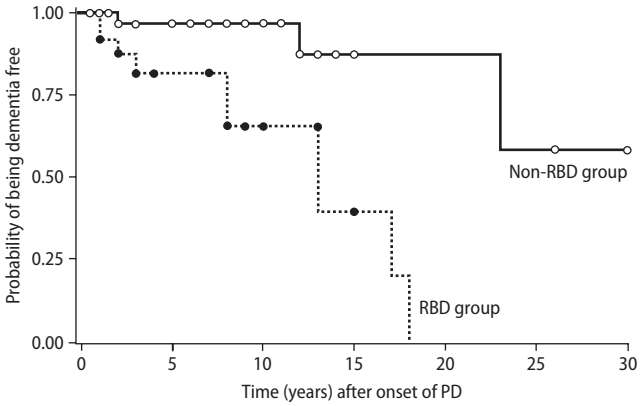

Fig. 1 Dementia free survival curve, comparing the frequency of dementia in the RBD and non-RBD parkinsonian patients (log rank test: p < 0.001)

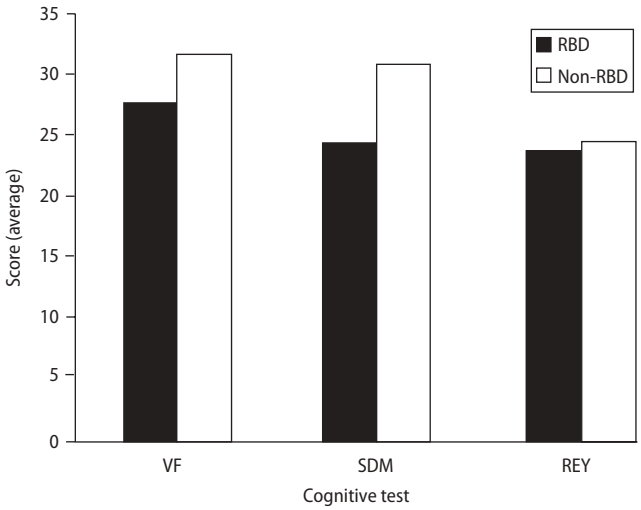

Fig. 2 Performance of PD patients with and without RBD in cognitive tests (*VF* verbal fluency test; *SDM* symbol digit modalities test; *Rey* Rey complex figures)

(mean ± SD = 27.8 ± 16.2; 24.61 ± 16.6) compared to the non-RBD (mean ± SD = 31.98 ± 14.75; 31.27 ± 17.14). (Fig. 2). However there was no significant difference in the performance of the cognitive tests in patients with and without RBD.

Discussion

We acknowledge the limitations in our study, in particular that the diagnosis of RBD did not involve PSG documentation, but we use a validated sleep questionnaire from the Mayo clinic (MSQ) [7, 8] which had been shown to have high sensitivity and adequate specificity for the diagnosis of RBD. The features described by patients and their informants were typical for RBD according to the published diagnostic criteria in 1997 [3]. Bed partners often explained how patients remembered

their dreams and gave detailed descriptions of them the following morning. Generally the patients complained of dreams in which they are attacked and in response they try to defend themselves, often resulting in aggressively punching and kicking in their sleep. In this study, RBD was clinically diagnosed in 37 % of the PD patients, which is similar to a previous study [19] based on polysomnography, where one-third of the PD patients were diagnosed with RBD.

The time of onset of RBD that we have recorded is supported by the interview of both the bed partner and the patient. The spouse often remembered precisely when she started sleeping in a different bed, or avoiding sleeping in a hotel, or being concerned at having guests overnight because of disrupted nights.

Our results have shown a male predominant pattern of RBD, which has been reported by previous studies [25, 27] and could be explained by the role of sex hormones. RBD has been reported to be associated with alpha synucleinopathies and in particular with dementia with Lewy bodies (DLB), in which an RBD frequency from 65 % to 80 % has been found [6, 9]. Our study is the first to show that RBD is significantly linked to the dementing process in the PD population. We found that PD patients suffering from RBD had a 6-fold higher occurrence of dementia than those without RBD. The dementia-free survival analysis also shows that the gap between the onset of PD symptoms and dementia is shortened in the presence of RBD, where 10 of the 24 RBD patients developed dementia with a median of 8.5 years (range: 1–18 years) and only 3 of the non-RBD patients developed dementia with a median of 12 years (range: 2–23 years) from the onset of PD. Therefore we suggest that PD patients with RBD have a higher risk of developing dementia earlier in the course of their illness.

Our findings show that RBD not only preceded or coincided but also followed the onset of PD motor symptoms in 17 (71 %) of the 24 RBD patients, and in particular in all the PD-D patients. Olson et al. [25] also reported a variable temporal pattern of occurrence of RBD. In addition, RBD followed the onset of dementia in 3 of the PD-D patients but the gap between dementia and RBD onset was shorter (median: 1 year, range 0.5–1 year). These patients had a more advanced age of PD onset (median: 70 years, range: 63–75 years) compared to the other groups. The exact pathogenesis of RBD is still unknown, but degeneration of one or several brainstem nuclei (substantia nigra, locus coeruleus and subcoeruleus complex, raphe nuclei and PPN) are likely to be responsible for RBD [20]. The pattern of progression of the disease, seen in our study, does not follow the proposed neuropathological staging of PD by Braak et al. [11], in which it was suggested that the disease process from the brainstem (stage 1 and 2) follows an ascending course in PD pathology to PD-D. In the cat, Lai and Siegel [22] had studied the anatomical link between PD and RBD and proposed that neuronal degeneration can begin in either part of the ventral brainstem and progressively extend to the rostral or caudal part of the brainstem, consistent with PD then RBD, or vice versa. We propose that there might be also an anatomical link between PD-D and RBD, involving cholinergic pathways, taking place both in RBD and Lewy body type dementia. Cholinergic deficit due to degeneration of the ascending pathways may contribute towards cognitive impairment and dementia in PD patients [16]. Therapeutically Rivastigmine (cholinesterase inhibitor) improves cognition in PD dementia [15] and PD-ND patients have been shown to develop cognitive decline when given anti-cholinergic drugs, whereas healthy controls do not, suggesting a subthreshold of cholinergic deficit in PD-ND patients [14].

In the present study, PD with RBD did not perform significantly worse on verbal fluency and symbol digit modalities compared to PD non-RBD, despite more demented patients in the PD-RBD group, which may be explained by the large standard deviation in each group. Some PD-ND patients performed poorly in the verbal fluency test and SDM, which are very sensitive tests for PD-dementia, but still have a MMSE superior to 25 and without an obvious executive function impairment in their daily life. Thus, patients in the earliest stage of dementia may not have been detected, which may explain the 20 % of PD-D in our study, which is slightly lower that the range (25–31 %) published from a meta-analysis on the prevalence of dementia in PD-D [2].

Idiopathic RBD patients have been reported to perform worse on neuropsychological tests compared to healthy controls, suggesting an existing impairment in visuospatial construction and learning [18], which in PD has been proposed to be caused by cholinergic deficits [1, 24]. The cognitive deficits in RBD patients are similar to those in patients with Lewy body type dementia, but different from AD [17].

For the reasons above, we suggest that a degenerative process taking place in the midbrain and in particular affecting the cholinergic and dopaminergic neurons of the brainstem nuclei, and progressing at a different pace in each patient, could explain the different patterns of clinical disease progression observed in our study and the significant co-incidence of RBD and dementia in the course of PD.

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