Early neurodegenerative biomarkers and clinical outcome in psychiatric patients with rapid eye movement sleep behaviour disorder: a prospective study

YK Wing*, SP Lam, VCT Mok, J Zhang, JMY Tsoh, EYL Leung

KEY MESSAGES

1. Patients who have rapid eye movement sleep behaviour disorder (RBD) as well as psychiatric illness (pRBD) may have a neurodegenerative outcome. The annual incidence of RBD was 1.9% in psychiatric patients. The incidence of Parkinson's disease in pRBD patients was 1.1%.
2. In most patients, RBD runs a persistent course. Despite symptomatic drug treatment, RBD symptoms and consequent sleep-related injury are still common.
3. Compared with psychiatric patients without comorbid RBD, pRBD patients have more prominent symptoms of depression and anxiety.
4. Persistent olfactory dysfunction is a feature in pRBD.

Hong Kong Med J 2018;24(Suppl 3):S24-8
HMRF project number: 01120326

[1] YK Wing, [1] SP Lam, [2] VCT Mok, [1] J Zhang, [3,4] JMY Tsoh, [5] EYL Leung

[1] *Department of Psychiatry, The Chinese University of Hong Kong*
[2] *Department of Medicine and Therapeutics, The Chinese University of Hong Kong*
[3] *Department of Psychiatry, Prince of Wales Hospital*
[4] *Department of Psychiatry, Shatin Hospital*
[5] *Department of Nuclear Medicine and Positron Emission Tomography, Hong Kong Sanatorium and Hospital*

* Principal applicant and corresponding author: ykwing@cuhk.edu.hk

This summary is based on a study first published in: Wing YK, Lam SP, Zhang J, et al. Reduced striatal dopamine transmission in REM sleep behavior disorder comorbid with depression. Neurology 2015;84:516-22.

Introduction

Rapid eye movement (REM) sleep behaviour disorder (RBD) is a novel and distinct parasomnia characterised by recurrent dream-enacting behaviours and polysomnographic features of a loss of normal REM sleep–related muscle atonia. In older patients, RBD (idiopathic RBD) is a precursor to neurodegeneration. Some patients with RBD who also have psychiatric illness (pRBD) show comparable clinical symptoms and abnormal REM-related electromyographic (EMG) muscle activities to idiopathic RBD patients.[1-3] The manifestation of RBD in these patients is increasingly recognised as an entity beyond a drug-induced condition. In addition, the REM-related EMG activities in pRBD patients are related to the severity of the mental illness. Preliminary results suggested that pRBD patients had more olfactory and dopamine dysfunction.[4,5] This study aimed to establish the longitudinal course and outcome of pRBD in terms of clinical symptoms, polysomnographic features, neurocognitive profile, and dopamine neurotransmission.

Methods

This was a prospective follow-up study of a cohort (including cases and controls) established in our previous cross-sectional case-control study in 2008.[1] It included a comprehensive phase 1 assessment of pRBD cases and two control arms that comprised psychiatric patients with no RBD symptoms (pControl) and healthy controls (hControl) to establish the longitudinal course, outcome, and neurocognitive profile of the participants. A subset of participants were recruited for phase 2, in which a neuroimaging study was conducted to identify any potential dopamine dysfunction.

We aimed to (1) establish the longitudinal course of RBD in terms of polysomnographic abnormalities of persistence and progressive increase in REM-related EMG activities, (2) compare the neurocognitive profile and any changes over time between case and control groups, and (3) explore the potential signs of early neurodegeneration (in terms of dopaminergic transmission abnormality) using neuroimaging. We hypothesised that: (1) RBD is a sustained and progressive condition in pRBD patients, and REM-related EMG activities will increase with time in these patients; (2) the neurocognitive profile would show a more prominent decline in the pRBD group over time compared with the control groups, particularly olfactory function and colour vision; and (3) pRBD patients would show early dopaminergic transmission abnormalities as demonstrated on neuroimaging.

Primary outcomes included the magnitude of

REM-related EMG activities and change in olfactory and visual neurocognitive profile, as measured by the olfactory identification test and Farnsworth-Munsell-100 Hue test. Secondary outcomes included neurocognitive performance (as measured by Mattis Dementia Rating Scale, Hong Kong List Learning test, Rey-Osterrieth complex figure, and trial-making test), dopamine transmission (quantified by neuroimaging), and incidence of new-onset clinical neurodegenerative diseases.

Data were analysed by SPSS (Windows version 22.0; IBM Corp, Armonk [NY], United States). Repeated measures analysis of variance by a general linear model was used for continuous data with a normal distribution. Skewed continuous data were log-transformed or square root–transformed for further general linear model analysis. For categorical data, a generalised linear model was used for repeated measurement. For variables in which only follow-up data were available (eg neurocognitive tests), analysis of variance or the Kruskal-Wallis test was used for three-group comparison, followed by post-hoc analysis, as appropriate.

Results

A total of 177 participants were recruited at baseline (Fig). One pRBD patient died and three healthy controls were excluded owing to subsequent development of mental illness (n=2) or pregnancy (n=1). Among 173 participants, 120 (69.4%) completed the follow-up study (phase 1) and comprised 39 pRBD patients, 38 pControls, and 43 hControls.

Longitudinal outcomes

At follow-up, of 39 pRBD patients, two men developed Parkinson's disease (PD) and had RBD symptoms at the age of 55 years. The overall prevalence and incidence of developing PD in pRBD patients were 5.1% and 1.1%, respectively. In 37 participants who remained free of any neurodegenerative disorder, 31 (83.8%) reported persistent RBD symptoms (defined as a RBD Questionnaire total score of ≥22 and a RBD Questionnaire factor 2 score of ≥8), and six (16.2%) reported no active RBD symptoms over the past year (five were female), of whom three were prescribed symptomatic drug treatment for RBD, namely clonazepam and melatonin. Regarding their antidepressant use at follow-up, two had stopped antidepressant use, two had switched the antidepressant from a selective serotonin reuptake inhibitor to a dopamine non-adrenaline reuptake inhibitor, and the remaining two had not altered their antidepressant regimen. For those with persistent RBD symptoms, 41.9% reported a history of sleep-related injury to themselves or bed-partners in the past year and 58.1% were taking medications for RBD symptoms.

For the pControl group, three participants developed RBD: two were taking the same antidepressant regimen at baseline and one had augmented treatment with two different classes of antidepressants. None was prescribed any medication for RBD symptoms. The prevalence and incidence of developing RBD in psychiatric patients were 7.9% and 1.9%, respectively. For the hControl group, there was no new incidence of RBD or neurodegenerative diseases.

Clinical and demographic characteristics

To compare the clinical characteristics of psychiatric patients with or without RBD, only patients without any change to their RBD status or neurodegenerative disease were included. Patients who developed PD in the pRBD group, and those who developed RBD in the pControl group were excluded from analysis.

There were no significant differences in sex or age at follow-up across the three groups (Table). The mean duration of follow-up was slightly longer in the pRBD group than the hControl group. Most (>90%) participants in the pRBD and pControl groups were diagnosed with major depressive disorder (MDD). There were five pRBD patients who had co-morbid

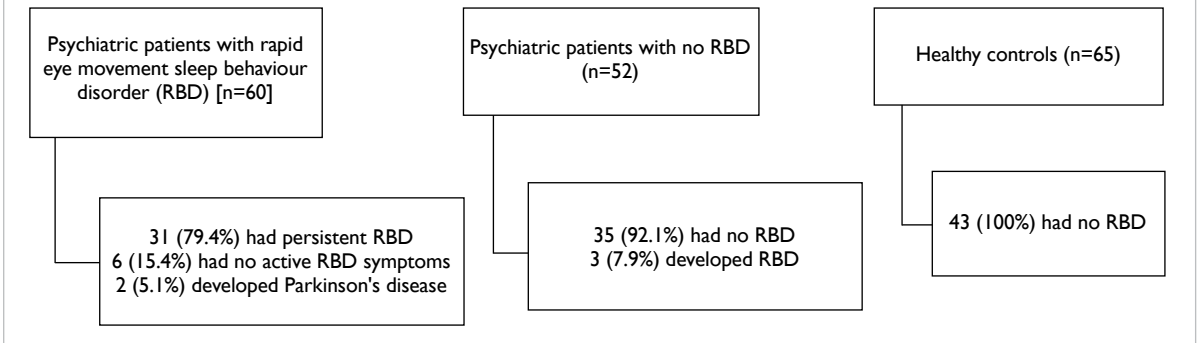

FIG. Flowchart showing longitudinal follow-up

MDD and post-traumatic stress disorder. Both pRBD and pControl groups had comparable psychotropic use, although the pRBD group had a higher use of mood stabilisers (32.3% vs 8.6%; P<0.05) and clonazepam (51.6% vs 5.7%; P<0.01).

Regarding clinical symptoms, the pRBD group had a significantly higher RBD questionnaire score than the other two groups at both baseline and follow-up (F(2,105)=122.8; P<0.01). The pRBD group also had a higher Hospital Anxiety and Depression Scale score (F(2,99)=27.386; P<0.01) and Beck Depression Inventory score (F(2,95)=22.427; P<0.01) than the other two groups at both baseline and follow-up. None of these variables showed any significant difference during the follow-up period. The Unified Parkinson's Disease Rating Scale motor score of pRBD patients at both baseline and follow-up was higher than that of the other two groups (F(2,77)=7.186; P<0.01); there was a significant change in the score during the follow-up period and there was a significant interaction between time and groups (F(2,77)=3.227; P<0.05). In particular, the pRBD group had a higher magnitude of increase in the score.

For total REM-related EMG activities, there was a significant difference during the follow-up period (F(1,99)=40.063; P<0.01) and the pRBD group had a significantly higher REM-related EMG score at both baseline and follow-up (F(2,99)=16.088; P<0.01) than the other two groups. Similar significant trends

TABLE. Clinical characteristics of study participants

Variable	Psychiatric patients with RBD (n=31)*	Psychiatric patients without RBD (n=35)*	Healthy controls (n=43)*	P value
Male	16 (51.6)	9 (25.7)	23 (53.5)	<0.05
Age at follow-up, y	49.8±10.4	52.7±11.0	50.1±7.3	NS
Education				<0.05
Illiterate/primary	4 (12.9)	9 (25.7)	2 (4.7)	
Secondary or above	27 (87.1)	26 (74.3)	41 (95.3)	
Follow-up duration, m	56.4±14.6	52.5±14.5	48.2±16.3	NS
Psychiatric diagnosis at baseline				
Major depressive disorder	29 (93.5)	33 (94.3)	-	NS
Bipolar affective disorder	2 (6.5)	1 (2.9)	-	NS
Post-traumatic stress disorder	5 (16.1)	0	-	<0.05
Schizophrenia/psychosis	0	1 (2.9)	-	NS
Psychiatric diagnosis duration, m	139.8±68.1	133.0±73.1	-	NS
Psychotropics at baseline				
Antidepressants	29 (93.5)	33 (94.3)	-	NS
Antipsychotics	6 (19.4)	7 (20.0)	-	NS
Mood stabiliser	6 (19.4)	3 (8.6)	-	NS
Benzodiazepines	17 (54.8)	5 (14.3)	-	<0.01
Non-benzodiazepine hypnotics	5 (16.1)	8 (22.9)	-	NS
Clonazepam	11 (35.5)	2 (5.7)	-	<0.01
Melatonin	1 (3.2)	1 (2.9)	-	NS
Psychotropics at follow-up				
Antidepressants	26 (83.9)	29 (82.9)	-	NS
Antipsychotics	9 (29.0)	12 (34.3)	-	NS
Mood stabiliser	10 (32.3)	3 (8.6)	-	<0.05
Benzodiazepine	17 (54.8)	4 (11.4)	-	<0.01
Non-benzodiazepine hypnotics	4 (12.9)	4 (11.4)	-	NS
Clonazepam	16 (51.6)	2 (5.7)	-	<0.01
Melatonin	1 (3.2)	1 (2.9)	-	NS
Prazosin	6 (19.4)	0	-	<0.01

Abbreviations: NS = not significant; RBD = rapid eye movement sleep behaviour disorder

* Data are presented as mean ± standard deviation or No. (%) of participants

were also found in tonic and phasic activities. There was no interaction between time and groups.

Neurocognitive markers

The pRBD group had more olfactory dysfunction at baseline than the pControl and hControl groups (41.9% vs 14.7% vs 16.3%; P<0.05). At follow-up, the prevalence of olfactory dysfunction remained higher in the pRBD group but not significantly (27.6% vs 17.1% vs 11.6%; P=0.22). More pRBD patients had persistent olfactory dysfunction at both baseline and follow-up (24.1% vs 5.9% vs 4.7%; P<0.05). Regarding colour vision, all three groups showed significant changes with time but there was no difference across the three groups.

For trial-making test, pRBD and pControl groups had significantly poorer performance than the hControl group (93.2±44.4 vs 108.7±51.7 vs 69.8±19.6; P<0.01), but the two psychiatric groups were comparable (post-hoc analysis: pRBD > hControl; P<0.05 and pControl > hControl; P<0.01). For the Mattis Dementia Rating Scale, the three groups showed a significant change over time (F(1,89)=5.070; P<0.05). For the Rey-Osterrieth complex figure for visual memory, the pControl group performed worse than the hControl group in both immediate recall (18.7±7.1 vs 24.2±6.2; post-hoc analysis: pControl < hControl, F=6.135; P<0.01) and delay recall tasks (19.4±6.1 vs 23.5±5.5; post-hoc analysis: pControl < hControl, F=4.943; P<0.01). In the Hong Kong List Learning Test for verbal memory, the pRBD and pControl groups had a poorer performance than the hControl group, but there was no significant difference between the pRBD and pControl group.

Neuroimaging findings

Thirty participants completed the triple neuroimaging study (14 pRBD patients, 6 pControls, and 10 hControls). The three groups were comparable in terms of age and sex. There was no significant difference in dopamine transmission (F-DOPA or Raclopide scan) among the three groups.

Discussion

The incidence of PD among pRBD patients was 1.1%. We could not conduct further analysis to explore the predictors for the conversion as the case number was small. Nonetheless, the two patients who developed PD were male and had onset of RBD symptoms after the age of 50 years. A longer term follow-up of this clinical cohort may help to identify potential predictors. The incidence of developing RBD in psychiatric patients was 1.9%.

RBD symptoms were persistent in about 80% of pRBD patients, even though almost 60% of them were prescribed symptomatic drug treatment. They had persistently higher REM-related EMG muscle activities at follow-up, compared with their control counterparts. Compared with pControls, pRBD patients had persistently more depressive and anxiety symptoms. Moreover, they persistently scored higher on the Unified Parkinson's Disease Rating Scale at baseline and follow-up, and the magnitude of increase with time was higher in pRBD patients than their control counterparts. The findings suggest that pRBD patients might harbour more subtle motor symptoms of Parkinsonism, although the severity of these symptoms did not reach the threshold for a clinical diagnosis of PD.

Various neurocognitive abnormalities have been identified as early markers for neurodegeneration in patients with idiopathic RBD. Nonetheless, the validity of these markers has not been examined in patients with co-morbid RBD and MDD. As patients with MDD are known to have neurocognitive deficits, there is a need to establish the neurocognitive profile of co-morbid RBD and MDD. We found no significant difference between pRBD patients and pControls in most neurocognitive tests, including those for memory, attention, and executive functions. Those with RBD symptoms were more likely to show persistent olfactory dysfunction. Olfactory function might be a more reliable marker in patients with co-morbid RBD and MDD. For dopamine transmission, we found no significant differences among the groups.

The study was limited by a small sample size to determine predictors for the conversion of neurodegeneration.

Conclusion

RBD in psychiatric patients may run a persistent course with a high prevalence of sleep-related injury despite symptomatic treatment. Similar to typical RBD in elderly patients, pRBD patients also had a higher chance of developing neurodegeneration. Compared with pControls, pRBD patients had more prominent symptoms of depression and anxiety and increased motor symptoms of Parkinsonism, and were more likely to have olfactory dysfunction and demonstrate a persistent increase in REM-related EMG activities.

Symptoms of RBD are prevalent and persistent in psychiatric patients. Patients with pRBD are associated with a higher prevalence of sleep-related injuries to themselves and bed-partners despite symptomatic drug treatment. In addition, longitudinal follow-up revealed a higher prevalence of persistent olfactory dysfunction and increased motor symptoms of Parkinsonism in pRBD patients.

Acknowledgements

This study was supported by the Health and Medical

Research Fund, Food and Health Bureau, Hong Kong SAR Government (#01120326). We dedicate this report to all the participants. The project could not have succeeded without their cooperation and participation.

Ethical Approval

The study was approved by the Joint Chinese University of Hong Kong - New Territories East Cluster Clinical Research Ethics Committee (Ref No: CRE-2012.577).

Declaration

The authors have no conflicts of interest to disclose.

References

1. Lam SP, Fong SY, Ho CK, Yu MW, Wing YK. Parasomnia among psychiatric outpatients: a clinical, epidemiologic, cross-sectional study. J Clin Psychiatry 2008;69:1374-82.
2. Lam SP, Zhang J, Tsoh J, et al. REM sleep behavior disorder in psychiatric populations. J Clin Psychiatry 2010;71:1101-3.
3. Lam SP, Li SX, Chan JW, et al. Does rapid eye movement sleep behavior disorder exist in psychiatric populations? A clinical and polysomnographic case-control study. Sleep Med 2013;14:788-94.
4. Postuma RB, Gagnon JF, Tuineaig M, et al. Antidepressants and REM sleep behavior disorder: isolated side effect or neurodegenerative signal? Sleep 2013;36:1579-85.
5. Wing YK, Lam SP, Zhang J, et al. Reduced striatal dopamine transmission in REM sleep behavior disorder comorbid with depression. Neurology 2015;84:516-22.