Rapid eye movement sleep behaviour disorder and psychiatry: a case-control study

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KEY MESSAGES

1. Rapid eye movement sleep behaviour disorder (RBD) in psychiatric patients is associated with a high prevalence of sleep-related injuries to self (60%) and others (65%). Early medical attention and intervention are indicated.

2. The aetiology of RBD in psychiatric patients is not simply a drug-induced condition, but involves a combination of clinical factors that include mood and sleep symptoms and psychotropic medications.

3. RBD in older persons is a precursor to neurodegenerative disorders. Olfactory dysfunction seen in the relatively young psychiatric patients may be a subtle sign of an early neurodegenerative process.

4. The aetiology of an underlying neurodegenerative process in psychiatric RBD patients should be further investigated.

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Introduction

Over the past two decades, a novel parasomnia—rapid eye movement (REM) sleep behaviour disorder (RBD)—has been recognised. It is characterised by a loss of normal REM-sleep-related muscle atonia. Sufferers may therefore 'act out' their dreams, usually of a violent nature, with consequent sleep-related injury (SRI) to themselves and bed-partners.[1,2]

The prevalence of typical RBD is 0.38% with an elderly male predominance. RBD is regarded as a precursor to synucleinopathy-related neurodegenerative diseases (such as Parkinson's disease and Lewy body dementia).[1] Approximately 26 to 92% of typical RBD sufferers will go on to develop a neurodegenerative disease. Early neurocognitive markers (eg olfactory dysfunction) have been identified in RBD patients who do not yet exhibit clinical signs of a neurodegenerative disease.

There have been increasing reports of RBD features in psychiatric patients. These patients were younger and mostly female, compared with typical RBD patients. A clinical epidemiological survey of psychiatric patients revealed that lifetime and 1-year prevalence of RBD symptoms was 5.8% and 3.8%, respectively, which was ten times more common than in typical RBD patients.[3] The condition was associated with prescription of the newer types of antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs).[3,4] One out of 20 patients prescribed a SSRI develop RBD in their lifetime.[3] The pathophysiological mechanism on how SSRIs, mental state, and individual vulnerabilities interact and culminate in attacks of RBD is unclear. It is unclear whether it is a spectrum or variant of typical RBD. Not all patients prescribed an SSRI develop the condition. It has been suggested that SSRIs are associated with loss of REM muscle atonia in asymptomatic patients. This study aimed to determine the clinical risk factors and the presence of early neurocognitive deficits in psychiatric patients with RBD.

Methods

This case-control study was conducted from October 2009 to September 2011. According to the International Classification of Sleep Disorder II criteria, 40 consecutive RBD patients were identified in a psychiatric clinic. They were matched with two control arms: (1) sex- and age-matched healthy controls from the community, and (2) sex-, age-, and diagnosis-matched psychiatric controls from the psychiatric clinic.

All subjects underwent structured clinical interview by trained interviewers for sleep and psychiatric diagnoses and questionnaires on sleep and mood symptoms, using the RBD questionnaire-Hong Kong (RBDQ-HK),[5] Beck Depression Inventory (BDI), and Hospital Anxiety and Depression Scale (HADS), as well as neurocognitive assessment including olfaction identification test, Chinese version of the mini-mental state examination (MMSE), and Mattis dementia rating scale.

All subjects also underwent one overnight video-polysomnographic study to measure the degree of loss of REM muscle atonia by REM-related EMG activities (REMREEA).[6]

Results

The three groups were comparable in terms of demographics. The two psychiatric groups were comparable in terms of psychiatric diagnosis and antidepressant usage (Table 1). However, co-morbid post-traumatic stress disorder (PTSD) was noted in seven RBD patients and one psychiatric controls. Psychiatric patients with RBD were also more likely to be prescribed benzodiazepines (including clonazepam), which are commonly prescribed for RBD. They also had the highest BDI and HADS scores, and more insomnia and recurrent nightmares.

Among psychiatric patients with RBD, 60% reported a history of SRI to self, 65% reported a history of attempted assault on bed-partner during their dream enactment, and 52.5% reported a history of falling out of bed during sleep. Most SRIs were mild (bruises or abrasions), but 12.5% were more severe (head injuries or lacerations).

The three groups were comparable in terms of sleep architecture (sleep efficiency, wake-after-sleep-onset, and REM density). However, healthy controls had shorter sleep latency and REM latency, longer slow-wave sleep, and lower apnoea-hypnoea index than the other groups (Table 2). Psychiatric patients with RBD had significantly higher total, tonic, and phasic scores in REMREEA, which is the pathognomonic sign of RBD. The REMREEA was associated with BDI and HADS scores (mood symptoms) and use of antidepressants (Table 3). Compared with phasic EMG activity, tonic EMG activity was associated with nightmare and prescription of benzodiazepines.

Overall, the healthy controls showed better neurocognitive performance than the other two groups in terms of olfactory identification test, MMSE, and the Mattis dementia rating scale (Table 3). Although psychiatric patients with RBD and psychiatric controls had comparable neurocognitive scores, there was a dosing relationship in olfaction identification test across psychiatric patients with RBD, psychiatric controls, and healthy controls (linear-by-linear association, P=0.002).

Discussion

In addition to its association with antidepressant usage, RBD in psychiatric patients was also associated with mood and sleep symptoms, and possibly early neurocognitive deficit. RBD results in SRI to self and bed-partners, and thus early attention, management, and exploration of the underlying pathophysiology is warranted. Although most believed that RBD was a drug-induced condition among patients taking antidepressants, in this study we found that the case and control groups differed significantly in mood and sleep symptoms, albeit comparable diagnoses and psychotropic prescriptions. The psychiatric patients with RBD had more anxiety and depressive symptoms, insomnia, and nightmares, all of which are associated with anxiety and mood disturbances. In addition, nightmare is a core symptom of RBD. Although most studies emphasise the importance of loss of REM-related muscle atonia as the pathophysiology of RBD, we suggest that nightmare also serves as a supratentorial drive to precipitate dream enactment features of RBD in susceptible subjects. Co-morbid PTSD in psychiatric patients with RBD is a common condition of RBD after exclusion of potential psychotropic effects. Although the exact pathological mechanism is not identified, it has been suggested that in PTSD, the decrease in the number of Locus Ceruleus neurons may account for both PTSD and RBD symptoms. We propose that RBD in psychiatric patients has a complex aetiology with several clinical factors (including mood and sleep symptoms) that increase the risk of developing RBD symptoms when taking psychotropic medications, particularly antidepressants. Simply considering RBD as a condition secondary to psychotropics use may be misleading, and may hinder further investigation and management of other contributory factors.

The severity of loss of REM-related muscle atonia was quantified by the REMREEA score. In normal physiology, REM sleep is associated with muscle atonia. Patients with RBD symptoms had a much higher REMREEA including both phasic and tonic activities. The increase in REMREEA in both psychiatric RBD patients and psychiatric controls compared with healthy controls may be in part due to the use of antidepressants that increase REM muscle activity during REM sleep. Nonetheless, psychiatric RBD patients still had significantly higher REMREEA than psychiatric controls. Benzodiazepines, particularly clonazepam, also affect phasic EMG activity. Future studies to investigate the effect of benzodiazepines and their dosage and length of use in psychiatric RBD patients are needed in order to determine their effect on the REMREEA. The presence of tonic REMREEA was noted in psychiatric RBD patients only. Long-lasting REM muscle activity (tonic activity), rather than short-lasting one (phasic activity), was independently associated with a reduction in striatal dopamine transporters, which is regarded as the pathophysiology of RBD. Our study further supports tonic activity as a hallmark feature of RBD.

Neurodegeneration is an important pathophysiological mechanism in typical RBD in the elderly population.[2] Early neurocognitive and neurobiological markers have been reported in

TABLE 1. Comparison of clinical characteristics in psychiatric patients with rapid eye movement sleep behaviour disorder (RBD), psychiatric controls, and healthy controls*

Clinical characteristics	Mean±SD or No. (%) of subjects			P value*			
	Psychiatric patients with RBD (group 1) [n=40]	Psychiatric controls (group 2) [n=40]	Healthy controls (group 3) [n=40]	1 vs 2 vs 3	1 vs 2	2 vs 3	1 vs 3
Age (years)	46.9±9.3	47.7±10.8	46.9±4.0	NS	NS	NS	NS
Male	12 (30)	10 (25)	12 (30)	NS	NS	NS	NS
Body mass index (kg/m²)	24.3±3.3	25.2±4.5	23.8±2.5	NS	NS	NS	NS
Smoking	11 (33.3)	4 (19.0)	3 (18.8)	NS	NS	NS	NS
Education level				NS	NS	<0.05	<0.05
Primary level or below	9 (22.5)	8 (20)	1 (2.5)				
Secondary level	22 (55)	24 (60)	29 (72.5)				
Tertiary level or above	9 (22.5)	8 (20)	10 (25)				
Psychiatric diagnoses (life time)	40 (100)	40 (100)	0	<0.01	NS	<0.01	<0.01
Major depressive disorder	36 (90)	38 (95)	0	-	NS	<0.01	<0.01
Bipolar affective disorder	3 (7.5)	1 (2.5)	0	-	NS	NS	NS
Anxiety disorder	1 (2.5)	1 (2.5)	0	-	NS	NS	NS
Co-morbid post-traumatic stress disorder	7 (18.4)	1 (2.5)	0	-	<0.05	NS	<0.01
Use of psychotropics	37 (92.5)	35 (87.5)	0	<0.01	NS	<0.01	<0.01
Antidepressants	33 (82.5)	33 (82.5)	0	-	NS	<0.01	<0.01
Selective serotonin reuptake inhibitor	25 (62.5)	21 (52.5)	0	-	NS	-	-
Serotonin-norepinephrine reuptake inhibitor	7 (17.5)	5 (12.5)	0	-	NS	-	-
Noradrenaline and selective serotonin antidepressants	0	3 (7.5)	0	-	NS	-	-
Tricyclics	1 (2.5)	7 (17.5)	0	-	NS	-	-
Benzodiazepine	21 (52.5)	4 (10)	0	-	<0.01	NS	<0.01
Clonazepam	13 (32.5)	2 (5.0)	0	-	<0.01	NS	<0.01
Non-benzodiazepine hypnotics	5 (12.5)	9 (22.5)	0	-	NS	<0.01	NS
Antipsychotics	11 (27.5)	8 (20)	0	-	NS	<0.01	<0.01
Mood stabiliser	4 (10.0)	3 (7.5)	0	-	NS	NS	NS
Polypharmacy (≥2 types)	29 (72.5)	28 (70)	0	-	NS	<0.01	<0.01
Beck Depression Inventory†	13.9±8.6	7.6±6.3	2.1±2.4	<0.01	<0.01	<0.01	<0.01
Hospital Anxiety and Depression Scale†	19.4±4.5	17.9±3.6	15.3±2.5	<0.01	NS	<0.01	<0.01
Anxiety subscale	8.9±2.5	8.8±2.5	7.1±1.8	<0.01	<0.05	<0.01	<0.01
Depression subscale	9.1±2.6	9.0±1.8	8.2±1.6	<0.05	NS	<0.05	<0.05
RBD questionnaire-Hong Kong†	45.1±14.7	7.6±5.3	6.0±5.2	<0.01	<0.01	NS	<0.01
Factor 1 dreams related	18.6±5.4	6.1±5.2	5.2±4.5	<0.01	<0.01	NS	<0.01
Factor 2 behavioural	26.5±10.9	1.5±2.2	0.8±1.7	<0.01	<0.01	NS	<0.01
Insomnia >3/week	11 (27.5)	8 (20)	1 (2.5)	<0.01	NS	<0.05	<0.01
Habitual snoring >3/week	0	0	0	-	-	-	-
Nightmares >1/week	19 (47.5)	2 (5.0)	1 (2.5)	<0.01	<0.01	NS	<0.01
Sleep-related hallucination >1/month	5 (12.5)	0	0	<0.01	NS	-	NS
Sleep paralysis >1/month	4 (10.0)	0	0	<0.05	NS	-	NS

* NS denotes not significant
† Kruskal-Wallis test (1 vs 2 vs 3) and Mann-Whitney U test (1 vs 2, 2 vs 3, and 1 vs 3)

TABLE 2. Comparison of polysomnographic data in psychiatric patients with rapid eye movement sleep behaviour disorder (RBD), psychiatric controls, and healthy controls

Polysomnographic data	Mean±SD			P value*			
	Psychiatric patients with RBD (group 1) [n=40]	Psychiatric controls (group 2) [n=40]	Healthy controls (group 3) [n=40]	1 vs 2 vs 3	1 vs 2	2 vs 3	1 vs 3
Sleep efficiency (%)	82.3±8.4	82.2±8.0	83.0±8.8	NS	NS	NS	NS
Wake after sleep onset (minutes)	63.0±37.5	68.1±34.6	64.2±33.2	NS	NS	NS	NS
Sleep latency (minutes)	22.1±18.7	17.2±12.2	14.5±12.1	NS	NS	NS	NS
REM sleep latency (minutes)	156.7±90.4	177.1±94.0	111.1±43.3	<0.01	NS	<0.01	NS
Stage 1 sleep (%)	48.6±26.4	37.9±21.1	29.3±15.5	<0.01	NS	NS	<0.01
Stage 2 sleep (%)	244.1±82.8	220.8±93.4	214.4±96.3	NS	NS	NS	NS
Slow wave sleep (%)	14.9±42.0	20.0±30.8	29.0±48.2	<0.01	<0.01	NS	<0.01
REM sleep (%)	78.2±37.3	91.5±56.3	88.7±19.7	NS	NS	NS	NS
REM density (%)	19.6±11.2	22.6±11.9	18.7±6.5	NS	NS	NS	NS
Apnoea-hypnoea index	11.0±13.9	10.3±12.0	6.5±7.8	NS	NS	NS	NS
Periodic leg movement index	8.5±15.3	9.4±16.3	4.9±12.5	NS	NS	NS	NS
REM-related EMG activity, chin (%)							
Total	16.0±18.1	5.6±4.7	3.5±2.9	<0.01	<0.01	NS	<0.01
Tonic	3.2±7.8	0±0	0±0	<0.01	<0.01	NS	<0.01
Phasic	12.6±15.9	5.6±4.7	3.5±2.9	<0.01	<0.01	NS	<0.01

* Kruskal-Wallis test (1 vs 2 vs 3), Mann-Whitney *U* test (1 vs 2, 2 vs 3, and 1 vs 3), and NS denotes not significant

TABLE 3. Comparison of neurocognitive data in psychiatric patients with rapid eye movement sleep behaviour disorder (RBD), psychiatric controls, and healthy controls

Neurocognitive data	Mean±SD			P value*			
	Psychiatric patients with RBD (group 1) [n=40]	Psychiatric controls (group 2) [n=38]	Healthy controls (group 3) [n=40]	1 vs 2 vs 3	1 vs 2	2 vs 3	1 vs 3
Mini-mental state examination	28.6±1.3	28.6±1.6	29.3±0.8	NS	NS	NS	NS
Alcohol sniff test	22.0±7.8	20.6±9.5	21.3±8.3	NS	NS	NS	NS
Olfactory identification test ≥4 items (%)	28 (70)	30 (78.9)	38 (95)	<0.01†	NS	NS	<0.01
Mattis dementia rating scale							
Total	138.6±5.5	138.9±5.2	141.6±2.0	NS	NS	NS	<0.05
Attention	36.4±0.8	36.4±0.8	36.9±0.4	<0.01	NS	<0.01	<0.01
Initiation	36.3±1.9	36.2±1.7	36.8±0.7	NS	NS	NS	NS
Construction	5.7±0.8	5.7±0.6	6.0±0.2	NS	NS	NS	NS
Conceptualisation	36.4±2.9	36.6±2.8	38.1±1.3	<0.01	NS	NS	<0.01
Memory	23.9±1.6	23.9±2.8	24.0±1.4	NS	NS	NS	NS

* Kruskal-Wallis test (1 vs 2 vs 3), Mann-Whitney *U* test (1 vs 2, 2 vs 3, and 1 vs 3), and NS denotes not significant
† Liner-by-liner association

idiopathic RBD, such as olfactory dysfunction and executive function abnormalities. In our study, these clinical tests were negative. A dosing effect was observed among the three groups in olfactory dysfunction, at which RBD patients had the poorest performance, but the difference was not significant between psychiatric RBD patients and psychiatric controls. These negative findings may suggest that neurodegeneration is not the underlying pathophysiology, or that our subjects were too young to develop prominent neurodegeneration. Our RBD patients were much younger than the older typical RBD patients (mean age, 46 vs 62 years). Among all early neurodegenerative markers documented in

RBD of an older population, olfactory dysfunction is a sensitive predictor that is measureable at least 5 years before the onset of clinical neurodegeneration with a slow progression at the preclinical stage.[7] The dosing effect in olfactory function may suggest a subtle deficit, and further studies are needed. In both RBD and Parkinson's disease, depression is a risk factor for neurodegeneration. Depression or its certain subtype may predispose individuals to the development of RBD, and the presence of mood and sleep symptoms as well as the use of antidepressants may trigger RBD symptoms in susceptible psychiatric patients. Further longitudinal follow-up is warranted to monitor the progress and course of any neurodegenerative outcome among psychiatric RBD patients.

Conclusion

The aetiology of RBD in psychiatric patients is not only drug-induced, but involves both mood and sleep symptoms. There may be early neurodegenerative components; further longitudinal follow-up of a psychiatric RBD cohort to identify any neurodegeneration is needed.

Acknowledgement

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