REM sleep behaviour disorder – more than just a parasomnia

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Background

Rapid eye movement (REM) sleep behaviour disorder (RBD) is a parasomnia characterised by loss of the usual muscle atonia that occurs during REM sleep, allowing patients to act out their dreams.

Objective

This article aims to draw attention to RBD, allowing early recognition and treatment.

Summary

As RBD patients are at high risk of hurting themselves and their bed partners while acting out their dreams, improving safety within the bedroom environment and treatment with exogenous melatonin or clonazepam are recommended. Longitudinal studies have shown that the onset of idiopathic RBD may be an early warning sign of specific neurodegenerative diseases.

Keywords

parasomnia; REM sleep parasomnia; sleep disorders

The normal pattern of sleep cycles through a number of differing stages, including non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. Dreaming mainly occurs during the REM stage of sleep and the brain appears highly active on electroencephalography (EEG), while a 'gating' mechanism in the brainstem leads to total relaxation of the body (atonia).

In REM sleep behaviour disorder (RBD), there is a loss of this muscle atonia where patients are able to act out their dreams, which can result in serious injury to the patient and their bed partner. In addition, the emergence of RBD in people over the age of 50 years has been flagged as an early indicator of neurodegenerative diseases, including Parkinson's disease (PD) and Lewy body dementia (LBD).

This article focuses on the role of the general practitioner (GP) in the diagnosis and management of RBD. It is anticipated that early recognition of RBD will be critical in the future use of neuroprotective agents to help tackle conditions like PD and LBD.

Case study

James was 54 years old when he was referred to a sleep disorder clinic because he broke his wrist diving out of bed while dreaming he was about to be hit by a train. The previous month he hit his wife while dreaming a tiger was attacking him. According to his wife, James had been having similar experiences for a couple of years but could not always remember his dream content. James was very healthy and not on any medication. His physical examination findings were unremarkable, as was neuroimaging. His sleep study ruled out sleep disordered breathing but revealed REM sleep without atonia (ie. muscle activity when the muscles should be at rest). James was commenced on clonazepam 0.5 mg, which relieved his dream enactment behaviour but caused some residual sedation during the day. Therefore, clonazepam was switched to melatonin 3 mg and within days James felt a significant improvement. James was followed up every year and after 3 years he developed PD.

Definition and classification of parasomnias

The stages of sleep are based on EEG appearances. Sleep stages alternate in a cyclic pattern every 60–90 minutes and are divided into NREM and REM sleep. The hallmark of parasomnia is any abnormal behaviour that evolves from sleep where motor or other arousal phenomena are expressed within a persistent sleep or partial sleep state.[1] Sleepwalking, confusional arousal and sleep terror are considered as disorders of arousal occurring from NREM sleep, whereas RBD occurs during REM sleep.

Idiopathic RBD as a REM parasomnia

In 1987, Schenck et al[2] reported a case series of 15 elderly patients with motor components occurring pathologically throughout the REM stage of sleep. The diagnostic criteria of RBD proposed by the International Classification of Sleep Disorders (ICSD-2) requires specific features in the sleep study as well as in the clinical setting (*Table 1*).[1] The most striking features of RBD relate to dream enactment behaviour with often purposeful limb movements and vocalisation, including shouting, swearing, crying or singing. Poor complex interaction with the environment whilst dreaming has been reported and although the patient may fall, they rarely climb out of bed, in contrast to the activity seen in sleepwalking.[3,4] Consequently, RBD can cause severe self-injuries as well as injuries to the bed partner.[5] Nearly 20% of patients have a lifetime incidence of head injury with unconsciousness caused by their RBD.[6] Pleasant and non-violent behaviour can also occur[7] and, importantly, the bed partner may provide the most crucial accounts as recall of the dream behaviour is inconsistently reported by patients.

RBD and neurodegenerative diseases

There is now strong evidence that RBD is linked to the development of neurodegenerative diseases, which are collectively known as the synucleinopathies.[8] These conditions include PD, LBD and multiple system atrophy (MSA), and share common neuropathological and clinical features of Parkinsonism. Longitudinal studies have shown that the risk of the idiopathic form of RBD (iRBD) converting to a Parkinsonian disorder varies from 40–80% over a 5–15 year period.[9–14] Several studies attempting to better predict the transition of iRBD to a neurodegenerative synucleinopathy have identified features such as constipation, postural hypotension, cardiac sympathetic denervation, deficiencies in olfaction, colour discrimination and cognition impairments as other potential red flags but, as yet, no reliable biomarkers have offered sufficient predictive value in clinical practice.[11,15,16] Given the growing burden of neurodegenerative diseases in our ageing population, early identification of RBD in general practice may offer a potential window for the use of future disease-modifying agents.[15]

Epidemiology of RBD

The exact prevalence and incidence of RBD in the community are currently unknown. Although RBD has been most commonly reported in males over the age of 50 years, there is growing evidence it can occur frequently in women but exists in a more subtle form.[17] The oft-quoted prevalence of 0.5% is probably an underestimation derived from studies in subjects aged 15–100 years old.[18] Indeed, more recent population-based studies in subjects aged 70–89 years old have reported higher prevalence levels (>8.9%), suggesting that it may be more frequent in the ageing population than previously thought.[19,20] Younger-onset RBD (<50 years) occurs more frequently in patients with narcolepsy and in those using antidepressant medications.[21]

Aetiology

RBD has a transient and a chronic form, the latter being idiopathic or associated with neurodegenerative diseases. As mentioned above, RBD will often predate the onset of the motor symptoms in PD but not all patients report this symptom, or may only develop it later in the course of the neurodegenerative process.[22]

Secondary RBD has been associated with narcolepsy whilst transient RBD has been reported in several neurological and toxic conditions such as lower brainstem lesions or Guillain–Barré syndrome, alcohol withdrawal and antidepressant use.[23,24] Therefore, careful assessment for such clinical features is needed before the diagnosis of the iRBD is made.

Diagnosis

The gold standard diagnosis of RBD relies on polysomnography (PSG), which shows excessive tonic chin electromyography (EMG) activity and excessive submental or limb twitching during REM sleep identified by EEG[25] (*Table 1*). Although visual scoring of the REM stage on PSG in RBD is recommended by a standardised method from the American Association of Sleep Medicine's *Manual for the Scoring of Sleep and Associated Events*,[26] it refers to qualitative scoring of the sleep study, the EMG and associated abnormal behaviours occurring in REM sleep as identified from the EEG. Numerous quantitative approaches, such as extensive EMG montages and an atonia index, have been proposed to objectively quantify the REM stage and the degree of loss of atonia.[27–28] However, consensus regarding these methods is lacking and they are not used in routine clinical practice.[29]

Given the limited access to PSG, attempts have been made to identify RBD from clinical interview as well as questionnaires. Postuma et al[30] have validated a single-question screening tool for RBD (RBD1Q) that could be easily applied in general practice to the patient and their bed partner. A positive answer to the RBDQ1, 'Have you ever been told or suspected yourself, that you seem to act out your dreams while asleep (for example, punching, flailing your arms in the air, making running movement etc.)?' should encourage the medical practitioner to consider the diagnosis of RBD as it offers good sensitivity (94%) and specificity (87%).[30] Other questionnaires, such as the REM sleep Behaviour Disorder Screening Questionnaire (RBDSQ)[31] or the REM Sleep Behaviour Questionnaires – Hong-Kong[32] are available for more detailed characterisation.

Differential diagnosis

RBD can be mimicked by different pathologies such as severe obstructive sleep apnoea (OSA), NREM parasomnia (eg. sleepwalking, sleep talking), nocturnal panic attacks, post-traumatic stress disorder and nocturnal seizures.[25,33]

Table 1. Diagnostic criteria of REM sleep behaviour disorder (ICSD-2)[1]

- Presence of REM sleep without atonia defined as sustained or intermittent elevation of submental EMG tone or excessive phasic muscle activity in the limb EMG.
- At least one of the following:
  - sleep-related injurious or potentially injurious disruptive behaviours by history
  - abnormal REM sleep behaviours documented on polysomnography.
- Absence of epileptiform activity during REM sleep unless RBD can be clearly distinguished from any concurrent REM sleep-related seizure disorder.
- Sleep disorder is not better explained by any other disorder, medical or neurological disorder, mental disorder, medication use or substance use disorder.

Physiopathology

Current animal models have suggested that RBD may be related to lesions of the REM sleep-regulating nuclei in the brainstem, especially within the pontine tegmentum and medial medulla.[20,22] These pathological changes would be in keeping with the proposed Braak-staging hypothesis of PD,[34] which initially involves these regions.

Treatment of RBD

The primary goal of treatment is to reduce injury to the patient and their bed partner whilst aiming to reduce unpleasant vivid dreams. Indeed, RBD-related injuries can lead to life-threatening conditions and have forensic consequences.[35] Securing the bed environment by physically removing hazards and lowering the bed has been recommended as the first-line treatment by an expert consensus.[36] Additionally, these guidelines propose that melatonin and clonazepam represent first-line medication treatment but their dosage and duration have not been standardised (*Table 2*). According to a recent survey, melatonin may be better tolerated than clonazepam and is therefore recommended especially in elderly or neurologically impaired patients.[37] Currently, both of these medications would need to be prescribed off-label if used for RBD.

Clonazepam is a long-acting benzodiazepine and should be used with caution as it can worsen concomitant obstructive sleep apnoea (OSA) and impair alertness, cognition and gait in older patients.[36,37] Melatonin is a hormone secreted by the pineal gland that modulates sleep initiation and circadian rhythms in humans; it has few side effects and is very well tolerated. Exogenous melatonin is used to treat age-related insomnia and circadian disorder but is not indicated for the treatment of RBD. Some authors have postulated a possible correction of an endogenous circadian desynchrony, although the drug dose used for patients with RBD is much higher than for circadian disorders.[38] To date only small case series or case reports support the efficacy of clonazepam and melatonin in RBD.[36] The only randomised double-blind, crossover, controlled trial in RBD included just eight patients over 4 weeks treated with 3 mg nightly of melatonin. Seven patients responded to melatonin with benefit confirmed by patients, bed-partner and PSG.[39] Recent best practice guidelines regard these treatments as Level B recommendations on the basis of limited evidence and clinical consensus.[36] Clearly, further randomised controlled trials are needed to assess the use of clonazepam and melatonin in RBD.

Table 2. Suggested treatment of RBD – recommended dose[36,37]

- Securing the environment
- Clonazepam 0.25–2 mg nightly
- Melatonin 3–15 mg nightly
- Combined treatment of clonazepam and melatonin are used in resistant cases

The role of the GP

Working in primary care, GPs are at the forefront of managing sleep disorders such as disturbed sleep, night-time agitation or violent parasomnia. Sleep-related questions are therefore important and should increasingly form part of the standard clinical practice in a GP consultation. Besides questioning on sleep-related breathing symptoms, a history of any dream-enacting behaviours and sleep-related injuries should be sought. Importantly, GPs can have a great impact on reducing sleep-related injuries, giving advice regarding securing the bed environment and minimising risk to the bed partner. A positive answer to the quick, single-question screen RBD1Q should encourage the GP to consider a diagnosis of RBD and refer the patient to a sleep physician or a multidisciplinary sleep clinic.

Conclusion

The recognition of RBD as a treatable parasomnia that could otherwise lead to serious injury is imperative in general practice. Furthermore, appreciating the significance of RBD as a potential pre-clinical marker of neurodegenerative disorders is an emerging concept that will be of increasing importance in an ageing Australian population. It is likely that any successful future neuro-protective strategies will rely on the confident identification of cases in their earliest stage.

Key points

- Any history of sleep-related injuries or dream-enactment behaviour should precipitate referral to a sleep centre for clinical investigation and sleep study.
- Bed partners often provide essential witness accounts of RBD behaviour.
- Reduce injury by improving the safety of the sleep environment if any dream-enactment behaviour is suspected.
- Avoid prescribing clonazepam in RBD unless severe sleep-related breathing disorder has been excluded or effectively treated.
- Careful assessment to exclude neurodegenerative conditions may require longer term follow up.

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Competing interests: None.
Provenance and peer review: Not commissioned; externally peer reviewed.

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