Idiopathic rapid eye movement sleep behaviour disorder: diagnosis, management, and the need for neuroprotective interventions

Alex Iranzo, Joan Santamaria, Eduardo Tolosa

Idiopathic rapid eye movement (REM) sleep behaviour disorder (IRBD) manifests as unpleasant dreams and vigorous behaviours during REM sleep that can result in injuries. Patients with IRBD have no known neurological diseases or motor or cognitive complaints; however, this sleep disorder is not harmless. In most cases, IRBD is the prelude of the synucleinopathies Parkinson's disease, dementia with Lewy bodies, or, less frequently, multiple system atrophy. Patients can show abnormalities that are characteristic of the synucleinopathies, and longitudinal follow-up shows that most patients develop parkinsonism and cognitive impairments with time. Thus, diagnosis of IRBD needs to be accurate and involves informing the patient of the risk of developing a neurodegenerative disease. It is extraordinary for a sleep disorder to precede the full expression of a neurodegenerative disease, which renders IRBD of particular interest in studies of the prodromal stage of the synucleinopathies, and in the development of neuroprotective interventions to stop or slow neurodegenerative deterioration before motor and cognitive symptomatology emerges. Such therapeutics do not currently exist, and thus represent an unmet need in IRBD.

Lancet Neurol 2016; 15: 405–19

Neurology Service, Multidisciplinary Sleep Unit, Hospital Clinic de Barcelona, IDIBAPS, CIBERNED, Barcelona, Spain (A Iranzo MD, J Santamaria MD, E Tolosa MD)

Correspondence to:
Dr Alex Iranzo, Neurology Service, Hospital Clinic de Barcelona,
Barcelona 08036, Spain
airanzo@clinic.ub.es

Introduction

Sleep is a physiological, recurring, and reversible state characterised by loss of consciousness, reduced responsiveness to the environment, and decreased body movement. Sleep is divided into two different states, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. Each state has different biochemical, neuronal, and metabolic properties. NREM sleep is characterised by slow eye movements, synchronised electroencephalographic activity, minimal mental activity, and partial loss of muscle tone. REM sleep, by contrast, consists of rapid eye movements, desynchronised electroencephalographic activity, dreams, and muscle atonia that precludes the sleeper from physically acting out their dreams, which could otherwise lead to injuries.[1]

Sleep can be affected in a number of ways, resulting in disorders that can be grouped into four categories: insomnias, hypersomnias, circadian rhythm changes, and parasomnias.[1] Parasomnias are abnormal behaviours and experiences during entry into sleep (eg, sleep paralysis), during NREM sleep (eg, sleepwalking), or during REM sleep.[2] REM sleep behaviour disorder (RBD) is a REM sleep parasomnia clinically characterised by unpleasant dreams (eg, being attacked or robbed) and vigorous behaviours in which the patients seem to be enacting their dreams (eg, punching, jumping out of bed, shouting). When recorded by nocturnal polysomnography, these behaviours occur during REM sleep and are associated with excessive electromyographic activity in the recorded muscles.[3–5] The pathophysiology of RBD is thought to result from dysfunction of the lower brainstem nuclei that modulate REM sleep muscle atonia (eg, subcoeruleus nucleus or magnocellularis nucleus).[6]

RBD can be classified as idiopathic (IRBD) or secondary (when a cause is identified). Patients with IRBD have no overt neurological disease and no relevant motor or cognitive complaints. Secondary RBD is associated with a neurological disorder (eg, neurodegenerative disorders, narcolepsy, or structural lesions in the brainstem), the introduction of certain drugs (eg, antidepressant drugs or β blockers), and alcohol withdrawal.[3–5] However, data indicate that IRBD is not a mere curiosity without neurological consequences. In contrast to the other parasomnias, follow-up of patients with IRBD shows that, with time, most patients develop the motor and cognitive features that lead to the diagnosis of a neurodegenerative disorder, particularly the synucleinopathies Parkinson's disease, dementia with Lewy bodies, or multiple system atrophy.[7–16] This finding has important implications with respect to the need for an accurate diagnosis of IRBD and patient management. The study of IRBD will improve our understanding of the prodromal stages of the synucleinopathies and will allow the testing of agents with putative neuroprotective effects for these neurodegenerative disorders. In this Review, we address the clinical characterisation, diagnosis, and management of IRBD and highlight the need to develop a strategy to slow or halt the degenerative process that presumably underlies this disorder. The pathophysiology of RBD and its association with various neurological disorders have been reviewed elsewhere.[6,17]

Epidemiology

The exact prevalence of IRBD in the general population is unknown. Epidemiological data are scarce because of the need for a large sample size to examine a disorder that is thought to be uncommon, and because diagnosis relies on polysomnography. In two population, questionnaire-based studies[18,19] of elderly people (aged 60–97 years), the prevalence of IRBD was estimated to be between 4·6% and 7·7%. These studies have probably overestimated the prevalence of IRBD because other disorders (eg, severe sleep apnoea, prominent periodic limb movements in

sleep, sleepwalking, and confusional awakenings in elderly people) can mimic RBD symptoms and give rise to false-positive cases. In the only two population-based studies in which polysomnography was used to confirm the diagnosis, the prevalence of IRBD was found to be between 0·3% and 1·15% in people older than 60 years.[20,21] Interestingly, none of the patients with IRBD in these two studies had sought medical attention because of abnormal sleep behaviours, suggesting that IRBD is an under-recognised entity. An additional finding supporting this view is that about 1% of patients with Parkinson's disease report RBD symptoms to their primary care physician before they are diagnosed with the disease,[22] yet up to 30% of these patients have these symptoms before the onset of parkinsonism.[23] Reasons for not seeking medical consultation include the belief that dream-enacting behaviours are normal and benign, poor knowledge of treatment options, unawareness of abnormal sleep behaviours in people who sleep alone, and embarrassment.[3,24]

Clinical features

Clinical characterisation of IRBD comes mostly from patients who self-refer to sleep centres. These patients might have a more severe form of the disorder, as the most common determinants of having sought medical help are sleep-related injuries, disturbing dreams, and bed partners' disrupted sleep. Other patients seek medical consultation after being made aware, from the media for example, that dream-enacting behaviours could herald a neurodegenerative disease.[3–5,24,25] Alternatively, IRBD is identified in patients who attend sleep centres for other reasons—for example, sleep apnoea or hypersomnia.[25] Irrespective of how patients are identified, the core clinical features of IRBD are abnormal sleep behaviours and unpleasant dreams.[3–5]

	Number of patients (N=212)
Self-awareness of sleep behaviours	121 (57%)
Motor behaviours	
Punching	183 (86%)
Kicking	173 (82%)
Falling out of bed	168 (79%)
Gesturing	155 (73%)
Hitting the nightstand	140 (66%)
Sitting up in bed	78 (37%)
Getting out of bed	52 (25%)
Assaulting the bed partner	47 (22%)
Walking	29 (14%)
Biting	20 (9%)
Measures of protection in bedroom	114 (54%)
Patients injured	128 (60%)
Bed partners injured	47 (22%)
Vocalisations	
Talking	203 (96%)
Screaming	191 (90%)
Moaning	135 (64%)
Laughing	115 (54%)
Crying	94 (44%)
Swearing	83 (39%)
Singing	31 (15%)

Data are n (%). Adapted from Fernández-Arcos and colleagues (2016).[25]

Table 1: **Abnormal sleep behaviour in patients with polysomnography-confirmed idiopathic rapid eye movement sleep behaviour disorder from the Multidisciplinary Sleep Unit (Hospital Clinic de Barcelona, Barcelona, Spain)**

Abnormal sleep behaviours

Patients with abnormal sleep behaviours show emotions during sleep such as aggressiveness, fear, annoyance, and, more rarely, joy—for examples, see table 1.[3–5,25] Clinical severity varies, with some patients showing a violent form of sleep behaviour and others a more subtle form. An interview with the bed partner is essential to assess the full repertoire of sleep behaviours, since many patients are completely or partially unaware of them. Typically, bed partners who see their partner's actions assume that they are acting out their dreams. Behaviours start abruptly, last from a few seconds to minutes, are performed with the eyes closed, and are mostly confined to the bed. Behaviours also include sitting up in the bed, falling out of bed,[3,25] or, in some patients, occasionally getting out of the bed and walking.[25] Patients might also display, albeit less commonly, non-violent, elaborate actions that look, for example, as if they are making a speech, trying to reach for something, eating, or riding.[26] If a patient wakes up during an RBD episode, they are easily oriented and might or might not recall a nightmare.[27] Injuries to the patient or to the bed partner are frequent and result from hitting the wall or the nightstand (figure 1), jumping out of bed, punching, kicking, biting, and occasionally attempting strangulation.[3,25] Sleep-related injuries include bruises, lacerations, sprains, dislocations, fractures, and, in extreme cases, subdural haematomas. Many patients report having to employ protective measures, for example, removing furniture, installing bed rails and barricades, or having their hands or trunk tied to the bed (figure 2).[3,25] In a few cases, violent behaviours can be lethal and carry medical–legal or forensic consequences.[28]

The clinical course of these abnormal sleep behaviours has not been examined in detail. Characterisation of onset and timecourse depend, in part, on the ability of the bed partner to watch their spouse's behaviours if they are disruptive enough to be awakened by them. A few patients report that their IRBD onset was related to a life event (eg, robbery, public humiliation, or surgery).[3,25] Other patients report a period of several years, or even decades, of sleep talking and limb jerks preceding the appearance of more complex actions such as loud vocalisations and violent behaviours.[3] Once IRBD is fully manifested, behaviours appear almost