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REM sleep behaviour disorder

and its link with neurodegenerative diseases

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A diagnosis of REM sleep behaviour disorder has important prognostic implications. The disorder is associated with synuclein-depositing neurodegenerative diseases and can be a harbinger of future decline and disability in those with these diseases.

Key points

- **The hallmark of REM sleep behaviour disorder (RBD) is the loss of the atonia that characterises REM sleep and which permits patients to act out dreams, often resulting in injury.**
- **Typically affecting older men, RBD is primarily diagnosed by history. Polysomnography is important in both confirming the diagnosis and ruling out differentials.**
- **Both nonpharmacological and pharmacological measures should be con - sidered in patients with RBD**
- **RBD confers a greater risk of Parkinson's disease, multiple-system atrophy and dementia with Lewy bodies, and in patients with these conditions, it confers a worse prognosis and more rapid progression of neurocognitive symptoms.**
- **Prompt referral and diagnosis of patients with suspected RBD is therefore important in most cases.**

Most people will display unusual behaviour during sleep at some stage in their lifetime. Whether it is sleep walking during childhood, the occasional episode of sleep talking or even the odd night terror, unusual behaviours during sleep are common and may not require treatment. The challenge for the primary care physician is discerning those behaviours that justify the need to refer patients to specialist services from those that can be noted and the patients reassured.

Parasomnias are undesirable physical phenomena that occur during sleep. As shown in the box on page 31, they can be categorised into three main groups based on when in the sleep cycle they occur. The stages of sleep are summarised in the box on page 31. Despite superficial similarities in some of the described activities, it is important to distinguish between

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PRIMARY SLEEP PARASOMNIAS[1]

Disorders of arousals from NREM sleep

- Confusional arousals
- Sleep walking
- Sleep terrors

Parasomnia disorders associated with REM sleep

- REM sleep behaviour disorder
- Nightmares (dream anxiety attacks)
- Recurrent isolated sleep paralysis
- REM-related painful erections

Other parasomnia disorders

- Catathrenia (nocturnal groaning)
- Bruxism
- Sleep-related rhythmic movement disorder
- Propriospinal myoclonus
- Somniloquy (sleep talking)
- Sleep enuresis
- Sleep-related dissociative disorders
- Exploding head syndrome
- Sleep-related eating disorder

ABBREVIATIONS: NREM = non-rapid eye movement; REM = rapid eye movement.

STAGES OF SLEEP

Sleep stages are categorised by brain activity seen on EEG and divided into four stages: stages 1, 2, 3 and rapid eye movement (REM) sleep.

As shown in the Figure below, the usual sleep pattern is cyclical, with the brain becoming progressively less active through stage 1 and 2 sleep and into slow wave sleep (stage 3) during the first hour or so. This is often followed by a period of REM sleep, before cycling back down into slow wave sleep. This cycle is usually repeated between three and six times a night. As the night progresses, the duration of each sleep stage changes. Slow wave sleep tends to predominate in the first half of the night, with REM sleep being more prominent in the second half of the night.

Slow wave sleep (stage 3) is deep restorative sleep and the brain is relatively inactive. Slow periodic tracings can be found on EEG taken during this sleep, from which it is named.

REM sleep is dream sleep and the EEG trace resembles the random rapid activity seen in awake patients. During REM sleep muscle tone is markedly reduced with exception of the respiratory muscles and ocular muscles. The function of REM sleep is unclear, although some believe that it may have a role in memory formation and retention.

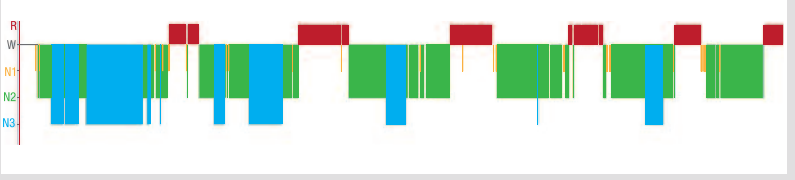

Figure. Stages of sleep during a six-hour period. R (red) = REM sleep; N1 (yellow) = stage 1 sleep; N2 (green) = stage 2 sleep; N3 (blue) = stage 3 sleep; W = awake.

parasomnias occurring during rapid eye movement (REM) sleep from those occurring during non-REM (NREM) sleep (such as slow wave arousal disorders).

This article focuses on the parasomnia REM sleep behaviour disorder (RBD), characterised by affected patients acting out dreams during REM sleep and which has been shown to be associated with synuclein-depositing neuro - degenerative diseases.

HISTORICAL AND CULTURAL PERSPECTIVES ON RBD

The concept of people 'acting out dreams' has been around for centuries. Parasomnia-like behaviour was described by early Roman and Greek authors. Depictions of strange behaviour in sleep can be found in Italian operas, Elizabethan plays and early modern literature. One of the most well known descriptions is in Cervantes' *Don Quixote*.[2]

'And they found him with the sword in one hand, stabbing everything as if he were fighting, and it was of note that he had his eyes closed, for he was sleeping and dreaming that he was in a battle against the giants.'[2]

Depictions of RBD can also be found in more contemporary media, most notably in Walt Disney films.[3] The characters exhibit typical features of acting out dreams and are late middle aged or elderly males. Interestingly, one character from the film *Lady and the Tramp* with RBD features was also losing his sense of smell and memory – both now established features of the neurodegenerative disorders associated with RBD.

From Cervantes' vivid description of RBD, it took the medical community 381 years to get up to speed when Schenck's group from the Minnesota Regional Sleep Disorders Center

DIAGNOSTIC CRITERIA FOR RBD[1]

The International Classification of Sleep Disorders (ICSD)-2 proposed the following minimal diagnostic criteria for RBD:

A. Presence of REM sleep without atonia, defined as sustained or intermittent elevation of submental EMG tone or excessive muscle activity in the limb EMG

B. At least one of the following:
   1. History of sleep-related injurious or potentially injurious disruptive behaviours
   2. Abnormal REM behaviours documented on polysomnography

C. Absence of epileptiform activity during REM sleep

D. Sleep disturbance not better explained by other sleep, medical, psychiatric or neurological disorder

TABLE. FEATURES DISTINGUISHING RBD FROM SLOW WAVE SLEEP AROUSAL DISORDER

Feature	RBD	Slow wave sleep arousal disorder
Awakening	Patients wake with a narrative, often very detailed. They can tell you why they were scared and are easily re-oriented once awake	Patients waken confused, often inexplicably terrified, with no narrative or simple flash imagery – e.g. spiders or snakes. They may be difficult to calm after waking
Behaviour	Behaviours can be varied and complex, corresponding to the reported dream narrative	Behaviours can be stereotypical
Associations with other conditions	Linked to neurodegenerative conditions when onset of symptoms occur in later life	No significant link to other conditions
Gender and age of patients	Older male predominance	No predominance
Sleep cycle	Occurs in later half of the night (more REM sleep)	Occurs in the first half of the night (more slow wave sleep)

published the first RBD case series in 1986.[4] This group reported a loss of the expected REM-related atonia in several patients with violent behaviour at night. Following these six cases were a steady stream of case reports and series and the term 'REM sleep behaviour disorder' was coined.

CLINICAL FEATURES AND DIFFERENTIAL DIAGNOSES

The hallmark of RBD is a loss of the muscle atonia that characterises REM sleep, which then permits the patient to act out dreams, often resulting in injury.[1] The diagnostic criteria for RBD according to the *International Classification of Sleep Disorders* are summarised in the box on this page.

The prevalence of RBD in the general population has been estimated to be about 0.5%.[5] The patient's history is the mainstay of diagnosis. Patients and their families describe unusual behaviour at night, often associated with a dream narrative. Patients who display harmful or aggressive behaviour are more likely to present for medical assessment. Often a series of injuries to themselves or a partner prompt presentation, and corroborative history from the bed partners is invaluable.

Patients with RBD are usually male, presenting in their 50s or above. They may have a family history of sleep disorders and a long prodrome of restlessness with prominent semi-purposeful nocturnal limb movements during sleep. Specific behaviours, purposeful movements and whether or not they are stereotypical (suggestive of a slow wave sleep disorder or seizure, not RBD) are important features of the history (Table). Patients with RBD are usually easy to orient once awake compared with those with NREM parasomnias, who often remain briefly disorientated. Unlike sleepwalkers, patients with RBD only occasionally stand up and walk, or include their environment as part of the behaviours (e.g. picking up a knife or eating). These less dramatic episodes of RBD usually go unnoticed, whereas the more distressing or dramatic episodes are seldom missed. An example of a patient with more dramatic episodes of RBD is described in the box on page 33.

The aggression and violence of the nocturnal behaviour usually bears little relation to the patient's daytime behaviour and personality. Those with violent nocturnal behaviours can be extremely distressed when they subsequently discover what they have done. Patients often delay seeking advice because of shame and embarrassment. Although some patients may complain of daytime sleepiness, the perceived quality of sleep may be entirely normal and sleep architecture on polysomnography may be preserved.

In younger patients, an alternative diagnosis should initially be sought and differential diagnoses such as seizure disorders should be excluded. RBD is also associated with narcolepsy and may be an early childhood symptom in patients

CASE STUDY. VIOLENT NOCTURNAL BEHAVIOUR IN AN ELDERLY MAN WITH RBD

David, a very placid and pleasant 72-year-old horse trainer, was referred to our clinic because of his strange nocturnal behaviour. Over the past decade or so he had often 'been up to mischief' at night, pottering around the house, opening drawers and talking to himself. He had two older brothers who had displayed similar behaviour. He reported several years of increased limb movements during sleep prior to the development of the more purposeful activities for which he was referred. His wife had just accepted his harmless odd behaviour and it was ignored.

The situation took a sinister turn when David began 'fighting guerrilla wars in his sleep.' For most people this would be alarming, but for David's wife the fact that he was attacking people in his sleep was terrifying because as a young man, before being a horse trainer, David had been in the Special Forces and trained to kill. David's wife moved to sleep in the spare room behind a locked door after she had been woken at 4 a.m. by David putting his hands around her neck.

David would wake with vivid and elaborate stories to explain what he had been doing. One day he awoke having run into a shelving unit that collapsed on top of him, and vividly described enemy soldiers throwing crates at him from a truck. He could describe how he found himself chasing the truck and could describe the enemies and their truck in great detail. He would often wake in a 'bunker' to find he was kneeling on the floor 'shooting' across the bed. Despite several injuries sustained walking into furniture and walls, it was the incident with his wife that prompted David to seek medical review.

Diagnosis

Polysomnography confirmed that David had loss of atonia during REM sleep, and significant amounts of movement. A diagnosis of RBD was confirmed.

Treatment

David's symptoms significantly improved soon after commencing clonazepam treatment, and his nocturnal behaviours dramatically reduced in intensity thereafter.

SOME POSSIBLE PRECIPITANTS OF ACUTE RBD[11,14]

Acute REM-rebound states

- Alcohol withdrawal
- Psychoactive drug withdrawal

Medications

- Antidepressants
  - SSRIs: citalopram/escitalopram, fluoxetine, paroxetine, sertraline
  - TCAs: clomipramine, amitriptyline, nortriptyline, imipramine
  - MAOI: phenelzine
  - Others: venlafaxine, mirtazapine, trazodone, bupropion
- Antipsychotics: haloperidol, olanzapine, risperidone
- Anticonvulsants: phenytoin
- Other drugs: bisoprolol, cimetidine, lithium, thyroxine, levodopa/carbidopa, selegiline, tramadol

Structural brain lesions (particularly if involving the brain stem)

- Ischaemic/haemorrhagic events
- Tumours
- Demyelinating disorders (multiple sclerosis)
- Encephalitis

ABBREVIATIONS: SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants; MAOIs = monoamine oxidase inhibitors.

with narcolepsy.[6] Antidepressant medications such as tricyclic antidepressants, monoamine oxidase inhibitors and selective serotonin reuptake inhibitors may precipitate episodes of RBD.[7-10] RBD can also occur transiently in association with REM rebound states such as alcohol, cocaine or barbiturate withdrawal (see the box on this page).[11,12]

Neuroimaging may be appropriate as idiopathic RBD can be associated with structural brain abnormalities.[14] It is unclear whether children and adolescents with persistent primary RBD are at a higher risk of neurodegenerative disease later in life and long-term follow up of these patients is currently recommended.[15]

THE ROLE OF POLYSOMNOGRAPHY IN DIAGNOSIS

The mainstay of RBD diagnosis is a careful history, but overnight polysomnography (PSG) is important. Characteristic PSG findings include excessive muscle tone found on chin or limb electromyography (EMG) or phasic EMG twitching during REM sleep. Simultaneous video monitoring may also capture some of the described behaviours during REM sleep.[1,16] However, the intermittent nature of RBD and potential differential diagnoses mean that PSG often has good specificity but poor sensitivity. PSG evidence of an alternative sleep disorder may confirm another diagnosis that presents with a similar history. The box on page 34 lists the differential diagnoses for RBD.

Obstructive sleep apnoea (OSA) is a much more prevalent sleep disorder and those with prominent REM-related OSA can often wake with a narrative when airflow obstruction occurs during REM sleep (i.e. dreams). Apnoeic episodes and relatively higher arousal thresholds during REM sleep can combine to cause unpleasant narratives. Patients with OSA and prominent REM-related symptoms may describe dreams of drowning or being choked and can awaken very

DIFFERENTIAL DIAGNOSIS OF RBD[17]

Slow wave arousal disorder
- Sleep walking
- Night terrors
- Confusional arousals

Secondary causes of arousals
- Obstructive sleep apnoea
- Periodic limb movement of sleep
- Gastro-oesophageal reflux disease
- Nocturnal seizures (consider frontal lobe seizures)

Psychiatric conditions
- Post-traumatic stress disorder
- Nocturnal panic disorder
- Conversion disorder

Rhythmic movement disorder

Malingering

disoriented and anxious. Polysomnographic diagnosis of REM-related OSA can be invaluable in these patients, and prompt treatment with continuous positive airways pressure should alleviate the symptoms.

RBD AND NEURODEGENERATIVE DISEASES

A diagnosis of RBD has important prognostic implications. There is increasing evidence that RBD is associated with synuclein-depositing neurodegenerative diseases (such as Parkinson's disease, dementia with Lewy bodies and multiple-system atrophy). Case series suggest that 38 to 65% of patients presenting with RBD over the age of 50 will go on to develop Parkinson's disease. RBD onset often precedes other neurocognitive symptoms by five to seven years,[17] but on the rare occasion by much longer.[18]

Longitudinal studies on patients with idiopathic RBD (those with no other neurodegenerative symptoms) show that they perform worse on cognitive and visual-spatial testing.[19] This has prompted some to question whether all patients with RBD in fact have some neurodegenerative process occurring, with those in the 'idiopathic' group having a slower progressing phenotype than those who manifest symptoms earlier.[20]

In patients with established synucleinopathies, RBD is common. It occurs in up to 60% of patients with Parkinson's disease and 80 to 100% of patients with dementia with Lewy bodies and multiple-system atrophy.[21-23] In patients with synucleinopathies, the co-diagnosis of RBD confers a poorer prognosis and earlier onset of more severe dementia.[24] A recent longitudinal study of 61 patients with Parkinson's disease found that 48% of those with RBD developed dementia during the four year follow-up period compared with none of those without ($p=0.14$).[25] Risk of developing dementia in patients with Parkinson's disease and RBD was shown to be 15% at two years, 29% at three years and 48% at four years.[25] Notably, typical movement features of parkinsonism disappear during RBD-associated complex behaviour in patients with synucleinopathies, suggesting motor efferents bypass the basal ganglia during REM sleep in these patients.

In contrast to the synucleinopathies, RBD is rare in other depositing neurodegenerative disorders such as Alzheimer's dementia or progressive supranuclear palsy. RBD is also rare in association with genetic neurodegenerative diseases such as Huntington's disease.[26]

MANAGEMENT

Not all patients with RBD require treatment, and treatment is dependent on the severity of disease. If the patient poses no threat to themselves or others, rarely has events and is not excessively tired due to their nocturnal activities, simple non-pharmacological measures may suffice.

Severity of RBD can be measured using frequency (rare or less than one episode per month to several episodes each night) and using violence and risk of physical injury. Severity may be difficult to assess and corroborative history from the bed partner is crucial. Movements typically occur in bed (unlike sleep walkers) and, therefore, the risk of injury to the bed partner is significant. A recent review of the literature found 41 reported cases of fatal/near fatal injuries, with choking/headlock being the most common.[27]

Nonpharmacological interventions

Nonpharmacological interventions such as maintaining a safe sleep environment for both the patient and the bed partner are important and should always be discussed. This includes removing dangerous objects such as guns and knives from the bedroom.

Other measures suggested are placing cushions or padding in the floor by the bed, putting the mattress itself on the floor, using a sleeping bag until the RBD is treated and padding the corners of furniture. Nocturnal alarms that deliver a calming message from a familiar voice have been shown to be helpful in a small case series of patients with refractory RBD.[28] Consideration should be given to the safety of the bed partner and they may elect to sleep in a different room until the RBD symptoms are controlled.[29]

Pharmacological measures

Initial pharmacological measures include a review of current medications with the aim of reducing or withdrawing those that may precipitate RBD. Pharmacological therapies recommended for RBD have not been tested in large randomised controlled treatment trials and have been found serendipitously, with the mechanism still to be elucidated. They are used off label for this indication.

Clonazepam (0.5 to 2 mg, 30 minutes before bedtime) is effective in reducing symptoms (both in frequency and intensity) in 50 to 90% of patients and patients usually respond rapidly.[29] Some, however,

MANAGEMENT OF RBD

Decide whether the patient needs treatment based on the following:

- Frequency of episodes
- Whether behaviour is physically or socially harmful
- Whether behaviour is posing a threat to themselves or others
- If there is tiredness due to patient's night-time activity

Recommend environmental factors to reduce injury risk

- Secure dangerous objects
- Place mattress on the floor and/or use a sleeping bag
- Lock windows
- Use nocturnal alarm
- Ensure safety of the bed partner

Initiate pharmacological treatment if required

- Clonazepam
- Melatonin

Consider other aspects, including:

- Ethical issues
- Long-term neurocognitive follow up

may experience unacceptable 'hangover' effects the next morning. The medication should be used with caution in patients with dementia, gait disorders or concomitant OSA. Case reports and very limited series exist using other benzodiazepines, but generally other benzodiazepines are not used.[29]

Melatonin (3 to 12 mg at bed time) has been shown to be efficacious in a small blinded randomised trial and, intriguingly, appears to partially restore normal atonia during REM sleep.[22,30,31] As melatonin is generally well tolerated with a benign side-effect profile, patients on clonazepam may be switched to melatonin when symptoms of synucleinopathies or dementia arise.

Other medications such as zopiclone, rivastigmine, acetylcholinesterase inhibitors and pramipexole have been reported to be helpful, but the evidence is currently limited to small case series and they cannot be routinely recommended.[29]

A summary of the management of RBD is given in the box on this page.

REFERRAL

Generally, all patients with suspected RBD should be referred to a specialist sleep physician for further assessment, diagnosis and initiation of pharmacological treatment if required and appropriate (see the box on this page). Prompt referral, diagnosis and education of treatment options may lead to improvements in quality of life for both the patient and the bed partner. In one case series, the mean diagnostic delay from first presentation to diagnosis was 8.7 years,[32] with lack of understanding of the disorder by patients and medical professionals cited as the main reason for delay.

All patients with RBD should also have a thorough neurological evaluation, which may include neurocognitive testing. Some advocate routine review by a neurologist once the diagnosis of RBD is made.

ETHICAL CONSIDERATIONS

RBD is strongly predictive of cognitive decline, dementia and the development of synucleinopathies. Symptoms of RBD typically precede other neurocognitive dysfunction by many years. Even in patients with so-called idiopathic RBD, the risk of developing dementia and other forms of synucleinopathies are increased. Given the devastating nature of these neurodegenerative disorders, debate remains as to how and when to best discuss this risk with the patient, bearing in mind that some patients with RBD never manifest neurodegenerative symptoms.

The increase in readily available medical information of varying quality via the internet has a significant bearing on this debate. Many patients will find out about the association between RBD and neurodegenerative disease whether or not their physician is comfortable discussing it with them. Discussing the association will also forewarn patients to re-present should they develop symptoms and will encourage monitoring of patients for symptoms.

WHEN AND WHY TO REFER PATIENTS WITH SUSPECTED RBD

When to refer

- Behaviours injurious to selves/others
- Socially embarrassing behaviours
- Fatigue and/or sleepiness thought to be due to nocturnal behaviours

Why refer?

- RBD is a distressing and potentially dangerous condition
- Simple, effective treatments are available
- To rule out, and monitor for associated neurodegenerative disorders

SUMMARY

RBD is a relatively rare condition with a broad differential in terms of both diagnoses and associations. Patient experience and symptoms also represent a broad spectrum, with some patients having minimal problems managing the condition and others being socially or physically harmed as a consequence of their disorder. Unusually, in some circumstances, RBD poses a threat to others.

RBD classically affects older men and is primarily diagnosed by history, but PSG is important in both confirming the diagnosis and ruling out potential differentials. Both nonpharmacological and pharmacological treatments need to be considered in patients with a diagnosis of RBD.

RBD is associated with synuclein-depositing neurodegenerative diseases

(notably Parkinson's disease, multiple-system atrophy and dementia with Lewy bodies) and can be a harbinger of future decline and disability. Prompt referral and diagnosis of patients with suspected RBD is therefore important in most cases so that treatment can be initiated and neurodegenerative disorders sought and monitored. MT

REFERENCES

1. American Academy of Sleep Medicine. International classification of sleep disorders, revised. Diagnostic and coding manual. 2nd ed. Westchester, Illinois: American Academy of Sleep Medicine; 2005.
2. De Cervantes M. The ingenious gentleman Don Quixote of la Mancha. De Francisco R; 1605.
3. Iranzo A, Schenck CH, Fonte J. REM sleep behavior disorder and other sleep disturbances in Disney animated films. Sleep Med 2007; 8: 531-536.
4. Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. Sleep 1986; 9: 293-308.
5. Ohayon MM, Caulet M, Priest RG. Violent behavior during sleep. J Clin Psychiatry 1997; 58: 369-376; quiz 77.
6. Schenck CH, Mahowald MW. Motor dyscontrol in narcolepsy: rapid-eye-movement (REM) sleep without atonia and REM sleep behavior disorder. Ann Neurol 1992; 32: 3-10.
7. Winkelman JW, James L. Serotonergic anti-depressants are associated with REM sleep without atonia. Sleep 2004; 27: 317-321.
8. Teman PT, Tippmann-Peikert M, Silber MH, Slocumb NL, Auger RR. Idiopathic rapid-eye-movement sleep disorder: associations with antidepressants, psychiatric diagnoses, and other factors, in relation to age of onset. Sleep Med 2009; 10: 60-65.
9. Olson EJ, Boeve BF, Silber MH. Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. Brain 2000; 123 (Pt 2): 331-339.
10. 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: 1374-1382.
11. Silber M. REM sleep behaviour disorder associated with barbiturate withdrawal. Sleep Res 1996; 25: 371.
12. Watson R, Bakos L, Compton P, Gawin F. Cocaine use and withdrawal: the effect on sleep and mood. Am J Drug Alcohol Abuse 1992; 18: 21-28.
13. Hoque R, Chesson AL, Jr. Pharmacologically induced/exacerbated restless legs syndrome, periodic limb movements of sleep, and REM behavior disorder/REM sleep without atonia: literature review, qualitative scoring, and comparative analysis. J Clin Sleep Med 2010; 6: 79-83.
14. Manni R, Ratti PL, Terzaghi M. Secondary ''incidental'' REM sleep behavior disorder: do we ever think of it? Sleep Med 2011; 12 Suppl 2: S50-S53.
15. Stores G. Rapid eye movement sleep behaviour disorder in children and adolescents. Dev Med Child Neurol 2008; 50: 728-732.
16. Consens FB, Chervin RD, Koeppe RA, et al. Validation of a polysomnographic score for REM sleep behavior disorder. Sleep 2005; 28: 993-997.
17. Mahowald MW, Schenck CH. REM sleep parasomnias. In: Kryger M, Roth T, Dement WC, eds. Principles and practice of sleep medicine. 5th ed. St Louis: Elsevier Saunders; 2011.
18. Claassen DO, Josephs KA, Ahlskog JE, Silber MH, Tippmann-Peikert M, Boeve BF. REM sleep behavior disorder preceding other aspects of synucleinopathies by up to half a century. Neurology 2010; 75: 494-499.
19. Fantini ML, Farini E, Ortelli P, et al. Longitudinal study of cognitive function in idiopathic REM sleep behavior disorder. Sleep 2011; 34: 619-625.
20. Mahowald MW. Does "idiopathic" REM sleep behavior disorder exist? Sleep 2006; 29: 874-875.
21. Sixel-Doring F, Schweitzer M, Mollenhauer B, Trenkwalder C. Intraindividual variability of REM sleep behavior disorder in Parkinson's disease: a comparative assessment using a new REM sleep behavior disorder severity scale (RBDSS) for clinical routine. J Clin Sleep Med 2011; 7: 75-80.
22. Boeve BF, Silber MH, Ferman TJ. Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. Sleep Med. 2003; 4: 281-284.
23. De Cock VC, Debs R, Oudiette D, et al. The improvement of movement and speech during rapid eye movement sleep behaviour disorder in multiple system atrophy. Brain 2011; 134: 856-862.
24. Lavault S, Leu-Semenescu S, Tezenas du Montcel S, Cochen de Cock V, Vidailhet M, Arnulf I. Does clinical rapid eye movement behavior disorder predict worse outcomes in Parkinson's disease? J Neurol 2010; 257: 1154-1159.
25. Postuma RB, Bertrand JA, Montplaisir J, et al. Rapid eye movement sleep behavior disorder and risk of dementia in Parkinson's disease: a prospective study. Mov Disord 2012; 27: 720-726.
26. Arnulf I. REM sleep behavior disorder: motor manifestations and pathophysiology. Mov Disord 2012; 27: 677-689.
27. Schenck CH, Lee SA, Bornemann MA, Mahowald MW. Potentially lethal behaviors associated with rapid eye movement sleep behavior disorder: review of the literature and forensic implications. J Forensic Sci 2009; 54: 1475-1484.
28. Howell MJ, Arneson PA, Schenck CH. A novel therapy for REM sleep behavior disorder (RBD). J Clin Sleep Med 2011; 7: 639-644A.
29. Aurora RN, Zak RS, Maganti RK, et al. Best practice guide for the treatment of REM sleep behavior disorder (RBD). J Clin Sleep Med 2010; 6: 85-95.
30. Kunz D, Bes F. Melatonin as a therapy in REM sleep behavior disorder patients: an open-labeled pilot study on the possible influence of melatonin on REM-sleep regulation. Mov Disord 1999; 14: 507-511.
31. Kunz D, Mahlberg R. A two-part, double-blind, placebo-controlled trial of exogenous melatonin in REM sleep behaviour disorder. J Sleep Res 2010; 19: 591-596.
32. White C, Hill EA, Morrison I, Riha RL. Diagnostic delay in REM sleep behavior disorder (RBD). J Clin Sleep Med 2012; 8: 133-136.

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