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Review

Rapid eye movement sleep behavior disorder and the link to alpha-synucleinopathies

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HIGHLIGHTS

- Rapid eye movement behavior disorder (RBD) is a well-described parasomnia, summarized here.
- RBD is associated with the development of the so-called alpha-synucleinopathies.
- We review this association, as well as treatment options for the symptoms of RBD.

ABSTRACT

Rapid eye movement (REM) sleep behavior disorder (RBD) involves REM sleep without atonia in conjunction with a recurrent nocturnal dream enactment behavior, with vocalizations such as shouting and screaming, and motor behaviors such as punching and kicking. Secondary RBD is well described in association with neurological disorders including Parkinson's disease (PD), multiple system atrophy (MSA), and other conditions involving brainstem structures such as tumors. However, RBD alone is now considered to be a potential harbinger of later development of neurodegenerative disorders, in particular PD, MSA, dementia with Lewy bodies (DLB), and pure autonomic failure. These conditions are linked by their underpinning pathology of alpha-synuclein protein aggregation. In RBD, it is therefore important to recognize the potential risk for later development of an alpha-synucleinopathy, and to investigate for other potential causes such as medications. Other signs and symptoms have been described in RBD, such as orthostatic hypotension, or depression. While it is important to recognize these features to improve patient management, they may ultimately provide clinical clues that will lead to risk stratification for phenoconversion. A critical need is to improve our ability to counsel patients, particularly with regard to prognosis. The ability to identify who, of those with RBD, is at high risk for later neurodegenerative disorders will be paramount, and would in addition advance our understanding of the prodromal stages of the alpha-synucleinopathies. Moreover, recognition of at-risk individuals for neurodegenerative disorders may ultimately provide a platform for the testing of possible neuroprotective agents for these neurodegenerative disorders.

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Abbreviations: DLB, dementia with Lewy bodies; EEG, electroencephalogram; IRBD, idiopathic RBD; LC, locus coeruleus; LDT, laterodorsal tegmentum; MCI, mild cognitive impairment; MRF, mesencephalic reticular formation; MSA, multiple system atrophy; Msec, millisecond; PD, Parkinson's disease; PGO, pontogeniculooccipital; PPT, pedunculopontine tegmentum; PRF, pontine reticular formation; PSG, polysomnogram; RBD, REM sleep behavior diorder; REM, rapid eye movement; RSWA, REM sleep without atonia; UPDRS, Unified Parkinson Disease Rating Scale.

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1. Introduction

Rapid eye movement (REM) sleep, which occupies approximately 20–25% of total sleep time, is a cyclical sleep state, occurring in intervals of 90–120 minutes during the night. Normally, during REM sleep, there is active inhibition of motor activity, which results in complete or near- complete muscle atonia. Atonia results from an interplay of multiple neurotransmitter systems, with a decrease in excitatory activity and increase in the inhibitory glycinergic and GABAergic premotor neuronal input to motor neurons.

However, the processes resulting in REM atonia can become disrupted, leading to REM sleep without atonia (RSWA) (Barone et al., 2015), which is a finding noted during an overnight polysomnogram (PSG) via abnormally increased electromyogram tone during REM sleep. REM sleep behavior disorder (RBD) is an abnormal condition consisting of RSWA in conjunction with a history of recurrent nocturnal dream enactment behavior.

The diagnosis of idiopathic RBD occurs when none of the conditions known to cause secondary RBD are present (see below), and when other conditions with possible abnormal nocturnal behaviors have been ruled out (obstructive sleep apnea or epilepsy, for example) (Iranzo and Santamaria, 2005; Peever et al., 2014). Potential risk factors for RBD include smoking, head injury, pesticide exposure, and having worked as a farmer (Postuma et al., 2012).

The diagnosis of secondary RBD occurs when there is an associated condition preceding it and likely contributing to its etiology (Peever et al., 2014), the most important being the alpha-synucleinopathies (Table 1). These conditions, including Parkinson's disease (PD), multiple system atrophy (MSA), dementia with Lewy bodies (DLB) (Gagnon et al., 2006; Manni et al., 2011), and pure autonomic failure (PAF) (Kaufmann et al., 2017) are so named because of the characteristic intracellular protein accumulation of alpha-synuclein, that may be visualized in a subset of synucleinopathies (for example PD and DLB) as Lewy bodies (Fig. 1) (Postuma et al., 2009; Classen and Schnitzler, 2010). It is unclear whether RBD is linked to the alpha-synucleinopathies via aggregated intracellular material, or through a common anatomic pathology (Ebben et al., 2012).

Of import is the fact that, in addition to secondary RBD occurring in the alpha-synucleinopathies, RBD can also precede the onset of alpha-synucleinopathy by decades (Iranzo et al., 2014). RBD is now therefore described as part of the "pre-motor" PD stage, and many individuals with RBD will develop PD (Iranzo et al., 2014; Visanji and Marras, 2015). As a result, an underlying pathology that impacts both REM atonia and midbrain dopaminergic centers has been postulated (Chen et al., 2013). This idea aligns with earlier publications postulating a spread of alpha-synuclein pathology through brainstem and other regions that could explain sleep abnormalities preceding motor abnormalities on an anatomical basis, the "Braak hypothesis" (Braak et al., 2003). Research into RBD therefore would ideally improve our ability to counsel patients, particularly with regard to prognosis, and would advance our understanding of the prodromal stages of the alpha-synucleinopathies. Moreover, recognition of at-risk individuals for neurodegenerative disorders may ultimately provide a platform for the testing of possible neuroprotective agents for these neurodegenerative disorders.

In this review, we address the underlying physiology of REM sleep, the putative pathophysiology of RSWA and RBD, the conditions known to be associated with RBD, including the alpha-synucleopathies, and the clinical factors that seem to herald the emergence of neurodegeneration in the context of RBD (Iranzo et al., 2016).

2. Rapid eye movement sleep and muscle control

REM sleep, first described in 1953 (Aserinsky and Kleitman, 1953), consists of low voltage fast electroencephalographic (EEG) activity, rapid eye movements, and muscle atonia. REM sleep is informally known as "dream sleep" due to the finding that waking subjects from REM sleep results in reports of dreaming (Dement and Kleitman, 1957). Initial experiments (Aserinsky and Kleitman, 1953; Dement and Kleitman, 1957; Jouvet, 1962) demonstrated the characteristic features of EEG and electromyogram (EMG) parameters that have come to define REM sleep. Normal REM sleep has been demonstrated to include corticohippocampal activation similar to wakefulness in addition to atonia of the postural muscles to prevent movement (Chen et al., 2013).

Evidence supports a number of key structures within the brainstem, whose activity is precisely integrated to produce REM sleep (Fig. 2). Proposed models of REM sleep physiology (Ng and

Table 1
Major clinical and pathological features of the alpha-synucleinopathies.

Neurological disorder	Major clinical manifestations	Pathology
Parkinson's disease	Bradykinesia, muscle rigidity, rest tremor, postural instability	Alpha-synuclein-containing intracytoplasmic Lewy bodies in neurons and Lewy neurites
Dementia with Lewy bodies	Dementia, fluctuating clinical status, hallucinations, parkinsonism	Alpha-synuclein-containing intracytoplasmic Lewy bodies in neurons and Lewy neurites
Multiple system atrophy	Autonomic dysfunction, parkinsonism, cerebellar signs in some	Alpha-synuclein containing glial cytoplasmic inclusions
Pure autonomic failure	Autonomic dysfunction	Alpha-synuclein-containing intracytoplasmic Lewy bodies in neurons and Lewy neurites

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