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Review Article

What Neurologists Should Know about REM Sleep Behavior Disorder and its Strong Association with Alpha-Synucleinopathy Neurodegenerative Disorders

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Abstract

James Parkinson's Description of REM Sleep Behavior Disorder and Freezing of Gate in Case VI:

REM Sleep Behavior Disorder Symptoms:

"His attendants observed that of late the trembling would sometimes begin in his sleep, and increase until it awakened him: when he always was in a state of agitation and alarm…"

"…when exhausted nature seizures a small portion of sleep, the motion becomes so violent as not only to shake the bed-hangings, but even the floor and sashes of the room…"

Freezing of Gate Symptoms:

"…whilst walking he felt much apprehension from the difficulty of raising his feet, if he saw a rising pebble in his path. He avowed, in a strong manner, his alarm on such occasions; and it was observed by his wife, that she believed that in walking across the room, he would consider as a difficulty the having to step over a pin."

[James Parkinson, 1817 monograph, "An Essay on the Shaking Palsy"].

Introduction

REM sleep behavior disorder

In 1986-1987, REM sleep behavior disorder (RBD) was identified and named at the Minnesota Regional Sleep Disorders Center; bedtime clonazepam, was found to be a highly effective therapy [1,2]. Among the 10 patients in the original series, 9 were males, and their mean age was 62 years. They had presented primarily on account of increasingly frequent and violent dream-enacting behaviors that had caused recurrent injuries to themselves and their spouses. Five had diverse neurologic disorders etiologically linked with the onset of RBD, and five were idiopathic at the time of RBD diagnosis [2]. The findings from these first 10 reported cases epitomize the classic clinical profile of RBD. The diagnosis of RBD was established by hospital-based video-polysomnography [VPSG].

The PSG hallmark of RBD consists of electromyography [EMG] abnormalities during REM sleep, referred to as "loss of REM-Atonia", or "REM-without Atonia" [RWA], featuring increased muscle tone and/or increased phasic muscle twitching. RBD represents how one of the defining features of mammalian REM sleep, viz. generalized skeletal muscle atonia, i.e. "REM-Atonia," can become severely impaired, permitting clinically consequential behavioral release during REM sleep [1-3]. A person with RBD moves with eyes closed, while attending to the dream environment and being completely unaware of the actual bedside surroundings, a highly vulnerable state [4,5]. VPSG monitoring can also document complex and aggressive behaviors during REM sleep that often can be correlated with simultaneous dreaming, as reported by the patient upon awakening. The enacted dreams often involve confrontation and aggression with unfamiliar people and animals, and the dreamer is rarely the primary aggressor. Otherwise, in the minority of cases there are abnormal behaviors during REM sleep without any associated dreaming. Injury to oneself or bed partner is common in RBD [4].

Idiopathic REM sleep behavior disorder as a harbinger of future Parkinsonism

As a larger group of idiopathic RBD [IRBD] patients was gathered and followed longitudinally at the Minnesota Regional Sleep Disorders Center, a surprisingly strong and specific association with eventual Parkinsonism became apparent. We reported in 1996 that 38% of a series of males >50 years old originally diagnosed with IRBD had developed a parkinsonian disorder [6], and then in 2013 we published extended longitudinal data on this series with findings that 81% [21/26] had developed a parkinsonian disorder--and no other condition [7]. The interval between the onset of IRBD to the emergence of Parkinsonism was 14+/-6 years [range, 5-29 years]. Thirteen patients had Parkinson's disease [PD], 4 had Dementia with Lewy Bodies (DLB), two had Multiple System Atrophy (MSA--PD with autonomic dysfunction), and two had the Lewy body variant of Alzheimer's disease (AD) (autopsy-confirmed). The two latter cases were notable because the clinical diagnoses in these two patients were AD and RBD, without any findings suggestive of Parkinsonism. And yet the autopsy findings found both AD and PD neuropathology. Identical longitudinal findings of IRBD patients were reported by the Barcelona group: 82% [36/44] converted at a mean interval of

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11.5 years [range, 5-23 years] from RBD onset [8]. The emergent neurological disorders closely matched our Minnesota findings: 16 patients had PD, 4 had DLB, 1 had MSA, and 5 had Mild Cognitive Impairment. The authors concluded that "in most patients diagnosed with IRBD, this parasomnia represents the prodromal phase of a Lewy body disorder...IRBD is a candidate for the study of early events and progression of this prodromal phase and to test disease-modifying strategies to slow or stop the neurodegenerative process." These bold findings have spurred a major, growing, multinational research effort, including the formation of the International RBD Study Group in 2009, which has published nine papers to date, including guidelines for assessing any future promising disease-modifying therapy [9]. The Montreal and Barcelona groups have identified the following prodromal markers that can indicate imminent conversion from IRBD to frank neurodegeneration: olfactory dysfunction; color vision dysfunction; serial DAT- SPECT abnormality showing progressive nigrostiatal dopaminergic dysfunction in IRBD [10,11].

Prior to the onset of Parkinsonism, patients with RBD have subtle, yet progressive, motor and gait abnormalities consistent with subclinical pathology [12]. While attempting to stand, motionless RBD patients have postural instability when distracted [13]. During gait initiation they also show abnormal force generation consistent with freezing of gait, and while walking there is a measureable decline in velocity and cadence with an increase in stride and swing variability [14,15].

Comorbid autonomic dysfunction is consistent with RBD as part of an evolving neurodegenerative disorder. Enteric neuron pathology manifests as constipation, and similar to hyposmia, when combined with RBD and impaired color vision, it predicts progression to PD. Cardiac scintigraphy has demonstrated sympathetic denervation among patients with RBD and heart rate orthostatic responses in RBD are blunted compared to controls and intermediate compared to those with PD [12].

By the time PD motor abnormalities develop; up to 90% of dopaminergic cells in the substantial nigra [SN] are dysfunctional. Neuroimaging has demonstrated progressive dopaminergic abnormalities in RBD prior to the onset of parkinsonian motor features [11]. Cholinergic denervation has been reported in RBD and, like cholinergic impairment in PD, these findings are correlated with cognitive decline [16]. Magnetic resonance imaging [MRI], functional MRI [FMRI], electroencephalography [EEG] and brain perfusion abnormalities have all demonstrated cortical abnormalities in RBD similar to those in patients with PD and DLB [17-19].

Not surprisingly, the three postmortem studies that have been published to date on IRBD have found Lewy body disease [12]. The reason why the spread of Lewy body pathology in some patients results initially (or exclusively) in clinical RBD but not in overt neurodegeneration is currently unknown, although a hypothesis has been presented, as reviewed [20].

Clearly, given the data just described, patients diagnosed with IRBD must be informed of the increased risk of future neurodegeneration and they should be urged to undergo longitudinal neurological examinations and cognitive screens for early detection of PD and/or dementia. This should also apply to younger adults diagnosed with RBD, as a retrospective study from the Mayo clinic found extraordinarily long intervals (up to 50 years) between RBD onset and Parkinsonism onset [21].

REM sleep behavior disorder and alpha-synuclein disorders

The prevalence of RBD varies amongst alpha-synuclein disorders: 30-50% in PD, 50-80% in DLB, and 80-95% in MSA [12-23]. The presence of RBD predicts the non-tremor predominant subtype of PD and a more rapid decline in motor and cognitive function, with greater disease burden [12,23]. RBD patients have a higher Hoehn and Yahr stage (increased severity), faster motor progression, and greater motor fluctuations [12-24]. Orthostatic hypotension and constipation are both more common in PD with RBD compared to PD alone [23,24]. In DLB, the presence of dream-enacting behaviors (DEB) is associated with an earlier onset of Parkinsonism and visual hallucinations [25]. RBD can also be found across the tauopathies, but with a much weaker association compared to the alpha-synucleinopathies [12].

Freezing of gait (FOG) is disabling and unresponsive to current medical and surgical PD therapy. It is characterized by transient episodes of absent forward movement during ambulation, gait initiation, or turning. Many of the same pontine regions implicated in the pathogenesis of RBD also mediate the pathophysiology of FOG. Among PD patients, those with RBD are most likely to have freezing of gait (FOG) and a higher frequency of falls [24].

Thus the presence of RBD in PD is associated with widespread increased PD morbidity, including increased level of PD motor impairment, increased level of cognitive impairment, increased visual hallucinations, increased autonomic dysfunction, and greater impairment in quality of life status. A recent study found that of 80 PD patients who were newly diagnosed with RBD and who were dementia-free at baseline, 34% [27/80] developed dementia (PDD) at 4.4 year follow-up [26]. RBD with PD at baseline in this study dramatically increased the dementia risk, with an Odds Ratio of 49.7 ($p = 0.001$). New light has recently been shed on the neuropathological basis for the increased morbidity of PD-RBD compared to PD without RBD [27]. Forty cases of PD with probable RBD (i.e. RBD detected by screening instruments, but without vPSG being performed) and 41 cases of PD without RBD (by screening instrument) had similar age at death (approximately 80 years old) and similar PD disease duration (approximately 14.5 years). Postmortem analyses found that PD-RBD patients had increased synuclein deposition in all regions examined, with significant differences found in 9 of 10 regions, compared to PD without (probable) RBD. PD-RBD patients had a greater density and range of synuclein pathology on autopsy.

The burden of disease on the patient and caretaker(s) is greatly increased in PD-RBD compared to PD without RBD. Furthermore, a recent study found an increased rate of impulse control disorders (ICDs--pathological gambling, compulsive sexual behavior, compulsive eating, compulsive shopping, and related behaviors, such as hobbyism) in patients with PD-RBD compared to patients with PD without RBD, with the risk for compulsive gambling being the most robust (fourfold) [28]. These findings indicate that is important to identify RBD in PD-even if the RBD is mild and does not necessitate pharmacotherapy, i.e. not an apparent clinical problem--because

of the increased risk for ICDs that would increase the burden of PD for the patient and family, on account of the potentially serious psychosocial, financial and legal consequences.

Clinicians managing PD patients should be well-informed about RBD, particularly since there is increased risk for recurrent injury or death from RBD. Even though RBD in PD is often mild to moderate in severity, "victim vulnerability factors" in RBD [5], such as bleeding disorder, anticoagulant therapy, osteoporosis, status-post surgical procedure, vertebral-spinal disorder, etc., can increase the risk for injury to the patient or bed partner, which should indicate the need for prompt therapy of RBD, even in mild cases. RBD can also lead to inadvertent CPAP non-compliance in PD patients with obstructive sleep apnea, as the CPAP mask can be repeatedly knocked off by RBD activity. Sleep disruption and secondary insomnia with daytime symptoms can affect the spouse/other caregiver who develops an "environmental sleep disorder" (3) from the sleep-disruptive RBD-related activity, adding to the burden for caregivers of PD patients. RBD detection can be facilitated by RBD screening questionnaires [29]. The clinical management of RBD in PD, and the current scientific issues embedded in these interlinked disorders, have recently been reviewed [30].

The strong link between RBD and Parkinsonism is scientifically understandable. The REM-atonia nuclei and circuits and the REM phasic motor nuclei and circuits are located in the brainstem extra-pyramidal region, and they have strong reciprocal connections with the motor nuclei degenerating from Parkinsonism. This topic has been recently reviewed in depth [20].

Finally, the thorny issue of terminology should be raised. Current opinion recommends that the evolution of PD to be split into "premotor" and "motor" phases, with clinical features such as anosmia, autonomic dysfunction, constipation, sleep disturbances (including RBD, periodic limb movements (PLMs) of sleep, and excessive daytime somnolence), etc., reflecting "premotor" manifestations; while the extrapyramidal features of resting tremor, bradykinesia, rigidity and postural instability reflecting the classic "motor" manifestations [20]. However RBD and PLMs are motor-behavioral disorders of PD--emerging during sleep. Therefore, a recent editorial suggested that this terminology be updated so that RBD and PLMs should be viewed as sleep-related motor activity and behaviors as legitimate PD prodromal signs, with the classic extrapyramidal signs of Parkinsonism being considered as wake-related motor activity and behaviors [20]. Furthermore, parkinsonian motor dysfunction during wakefulness subsides during REM sleep in RBD such that hypokinetic dysarthria is replaced by loud and coherent commands or screams, and the bradykinesia and tremor are replaced by fast and fluid movements of the limbs devoid of tremor, a striking wake-sleep state dependent behavioral dissociation [31]. So although it may be abnormal to develop RBD, in the context of PD and MSA (with findings similar to just described for PD [32]), there is considerable normalization of behavior and vocalization during REM sleep in RBD, compared to compromised waking motor capabilities in these neurologically impaired individuals.

Conclusion

RBD is situated at a strategic and busy crossroads of sleep medicine, neurology, and the neurosciences. RBD offers great breadth and depth of research opportunities, including extensive inter-disciplinary and multi-national research opportunities, as exemplified by the ongoing activities of the International RBD Study Group, with yearly symposia and publication of peer-reviewed journal articles. Neurologists are encouraged to keep abreast with new findings related to RBD and neurodegenerative disorders and their clinical management, especially considering how the literature on RBD continues to grow exponentially [33].

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