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REM sleep behavior disorders in Parkinson's disease and other Parkinsonian disorders

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1. Introduction

In the seventies, Jouvet and Delorme [1] documented the crucial role of tegmental pontine structures in generating abnormal REM sleep without atonia in the animal, a finding confirmed by further lesional studies [2]. Electrolytic lesions of the dorsal pontine tegmentum in the cat created REM sleep without muscle atonia, and the animals displayed dream-enacting motor behavior.

Though not uncommon in humans, a dissociated REM sleep condition comparable to the animal model was formally identified by Schenck and Mahowald 20 years later [3] and named REM sleep behavior disorder (RBD). Since 1990 RBD has been included in the International Classification of Sleep Disorders (ICSD) within the REM sleep parasomnias [4]. Two forms were formerly described—acute and chronic—but the term RBD primarily refers to the second, the acute form often being associated with drug abuse [5,6] or drug and alcohol withdrawal [5–8] and part of a complex dissociated circadian condition of wake and sleep [5,8,9]. Thus, the term RBD more properly refers to a condition in which the dysfunction is confined to REM sleep, and the sleep-wake pattern as well as the sleep architecture are grossly preserved, as we typically find in the chronic form.

RBD is characterized by intense motor or verbal paroxysmal dream-enacting episodes arising in REM sleep during loss of muscle atonia, as indicated by elevated chin electromyography (EMG) tone [6,10,11]. Clinical manifestations range from increased muscle twitching and jerks to complex, organized and finalistic motor and verbal activities leading to enacted dream behavior. Such motor and verbal manifestations, as well as the content of dreams, are often fearful and violent and can lead to physical injuries to partners and patients alike. When patients wake during the episode they always recall a dream. The first episode usually appears at least 1 h after falling asleep, coinciding with REM sleep, and episodes may occur intermittently during the night. Due to the increase in REM sleep in the last third of the night, episodes are often more intense during the early morning hours and are accompanied by the recall of vivid, fearful dreams. Like other REM sleep-parasomnias, autonomic activation is not dramatic. Episode frequency ranges from one or a few attacks per month to one or more every night, but usually increases over the years.

RBD is more frequent in males; mean age of onset, ranging between 55 and 60 years of age, can be 'idiopathic' or linked with neurological diseases. Isolated RBD can be the tell-tale sign of a pontine lesion [12–15], but more often indicates a neurodegenerative disease, particularly a Parkinsonian syndrome. Clonazepam is the drug of choice in RBD, in either 'idiopathic' or symptomatic cases, and withdrawal of treatment usually leads to reappearance of attacks [10,16].

Following the original series by Schenck and Mahowald, in which RBD was associated in 42.9% of cases with neurological diseases such as Parkinson's disease (PD),

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Shy-Drager syndrome, olivopontocerebellar atrophy, dementia, ischemic encephalopathy, alcoholism, multiple sclerosis, brainstem astrocytoma, Guillain-Barré syndrome and narcolepsy, RBD has most often been reported in association with PD [17], Lewy body disease (LBD) [18–21] and multiple system atrophy (MSA) [22–25]. The ten-year follow-up of the original patients with 'idiopathic' RBD reported by Schenck et al. disclosed the appearance of a Parkinsonian disorder in 38% of patients, confirming that 'idiopathic' RBD responsive to clonazepam can precede the clinical onset of these neurodegenerative diseases [26]. The common association of RBD with extrapyramidal disorders and the finding that RBD can herald the clinical onset of at least a subgroup of Parkinsonisms, the so called 'synucleinopathies' [27], determined a growing interest in this disorder in recent years.

2. Diagnostic criteria for RBD

According to the ICSD [4], the diagnosis of RBD is based on the following minimal clinical criteria: limb or body movement associated with dream mentation (criterion B) and at least one of the following (criterion C): (1) harmful or potentially harmful sleep behaviors; (2) dreams that appear to be 'acted out'; (3) sleep behavior that disrupts sleep continuity. Most of the prevalence studies of RBD in Parkinsonian patients are questionnaire surveys or semi-structured clinical interviews based on the above criteria and do not account for the gold standard tool for RBD: polysomnography (PSG). PSGs with extended montage, including at least EEG, right and left EOG, surface EMG from mylohyoideus, right and left tibialis anterior and right and left extensor digitorum communis muscles, are indeed crucial to confirm the diagnosis [6]. In fact, the diagnosis of RBD is certain only when the clinical and PSG criteria formulated by Mahowald and Schenck are fulfilled: (1) an excessive increase in chin EMG tone or excessive limb or chin EMG twitching, irrespective of chin EMG tone, during REM sleep, associated with (2) abnormal behavior during REM sleep or a history of injurious or disruptive sleep behaviors. Due to the abundance of sleep-related motor disturbances in PD, and their possible overlap with clear-cut RBD or with the sole polygraphic finding of REM sleep without atonia (RWA), the PSG analysis itself is often difficult, even with an extended montage, and requires a skilled trained reader [28]. The video-PSG documents the dream-enacting behavior with the typical EEG and EMG findings, finally helping to solve the most challenging cases.

The large population studies based on questionnaire surveys do not reach unequivocal results. Moreover, the discrepancies in the frequency of RBD disclosed by clinical versus PSG studies of Parkinsonian patients suggest that clinical data alone are overly lax, that in general they tend to underestimate the frequency of RBD in Parkinsonian patients, and that the diagnosis of RBD in these subjects requires PSG. Alternative methods to PSG (i.e. actigraphy) may help to identify RBD episodes in 'idiopathic' RBD but do not offer unequivocal findings when RBD overlaps with other sleep disorders, as often happens in Parkinsonian patients (Fig. 1).

3. RBD and MSA

Multiple system atrophy (MSA) is characterized by any combination of autonomic failure with Parkinsonism, or with cerebellar and pyramidal signs and absent or poor response to levodopa. Laryngeal stridor during sleep is also common [29]. Although it is not included in the diagnostic criteria for MSA, RBD is the most common sleep-related disorder associated with this disease [25]. Since the 1980s several MSA cases with RBD have been reported, and several case

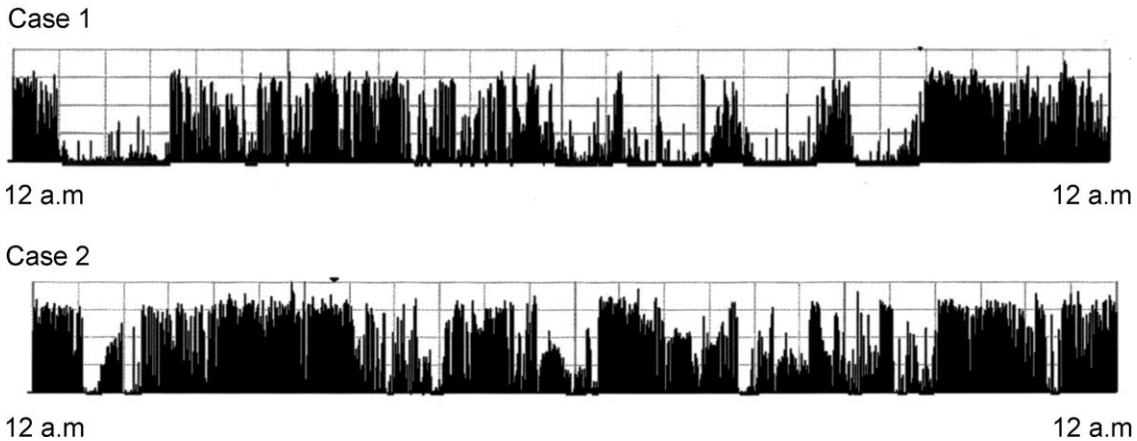

Fig. 1. Twenty four hour actigraphic recording of a patient with 'idiopathic' RBD (Case 1) and a patient with MSA and RBD (Case 2). *Case 1*: in the presence of a history of acted out dreams, the repetitive increase in muscle activity during the night, more intense in the early morning hours, probably coinciding with REM sleep, strongly suggests a RBD. *Case 2*: the patient complained of insomnia and agitated nocturnal sleep, with fearful vivid dreams; nevertheless the widespread motor activation during the whole night does not directly suggest a RBD.

reports have indicated that RBD represents an early, unusual symptom of MSA [24,25]. In their 10 year follow-up study Schenck and coworkers suspected that at least some 'idiopathic' RBD patients developing a Parkinsonian disorder might later develop MSA, but the follow-up was too short to confirm a diagnosis [26]. Clinical RBD was present in 69% of a series of 39 consecutive MSA cases [25], preceding the appearance of motor or autonomic symptoms of MSA in 44% of this sample. On video-PSG, 90% of these patients had RBD, and all REM stages were characterized by persistent RWA. Other sleep disorders were sleep apnea (15%), laryngeal stridor (20%), and periodic limb movements (PLMs) during sleep (26%), establishing that RBD represents the most common clinical sleep manifestation in MSA and confirming that it frequently heralds the appearance of other symptoms by years.

RBD is also a specific sign of MSA in primary autonomic failure patients [30]; the recognition of RBD thus has a prognostic value in the evaluation of these syndromes. Another point raised in our paper [30], and confirmed by subsequent studies [31,32], is that RBD remains underestimated by both clinical judgment and targeted structured interview. This is probably due to the frequent coexistence in MSA patients of several potentially confounding sleep disorders, but also to the weakness of the diagnostic ICSD clinical criteria. In fact, an abnormal activation during RWA, not only of limb muscles but also of cranio-facial and oro-facial muscles, possibly associated with sleep-talking or vocalization, is common [31] in MSA patients without clinical RBD, but is a clear-cut proof of RBD. On the other hand, the atypical muscular activations and respiratory noises often encountered in MSA patients may represent further clinical confounding factors, mimicking or masking RBD. Thus, PSG readers must also distinguish RBD from other masking polygraphic findings, more often present during NREM than REM sleep in MSA patients, such as PLMs during sleep [25,33], respiratory and skeletal muscles hyperactivity [34], and laryngeal stridor during sleep [35].

4. RBD and LBD

LBD, the second most common form of degenerative dementia in the elderly, is clinically characterized by fluctuating cognitive impairment, prominent attentional deficits, visuospatial dysfunction, visual hallucinations and eventually extrapyramidal signs. RBD is considered an additional feature supportive for diagnosis [36]. In fact, several case reports have suggested that RBD may also herald or accompany LBD. Isolated RBD has been reported to precede by decades the clinical onset of LBD, associated or not with Parkinsonism [37]. Finally, diffuse LBD has also been reported as an incidental post mortem discovery in a neurologically normal old man [19].

The association of LBD and RBD has been confirmed in two large studies [20,21]. The first assessed a group of 37 elderly patients with RBD and degenerative dementia associated (54%) or not (46%) with Parkinsonism [20]. Thirty-four (92%) patients met the clinical criteria for possible or probable LBD; three patients underwent pathology examination and all had LBD. RBD heralded or was concomitant with dementia in 35/37 patients and was confirmed on PSG. No demographic, clinical or neuropsychological differences split the groups of patients with and without Parkinsonisms. In the second study, the same authors explored the neuropsychometric differences between two groups of 31 patients each, one group with degenerative dementia and RBD on PSG, the other group with clinical and neuropathologically confirmed Alzheimer's disease without brainstem Lewy bodies [21]. Thirty/31 patients with dementia associated with RBD met the clinical criteria for possible or probable LBD. Taken together, the above studies indicate that RBD, even isolated, may underlie a Lewy bodies pathology and can herald LBD. Thus, the association degenerative dementia-RBD strongly suggests LBD.

5. RBD and PD

Early preliminary studies suggested that RBD may also herald PD in elderly males [38] and may respond to levodopa [17]. RBD has also been described in a case of juvenile PD, but associated with narcoleptic features such as excessive daytime sleepiness and sleep onset REM sleep periods at multiple sleep latency test (MSLT) [39]. Furthermore, subclinical RBD has been found on PSG in both treated and untreated PD [40]. Overall, RBD in elderly males in the PD population seems to predominate in cases with a longer disease course and a higher disease severity. Nevertheless, the real frequency of RBD in the PD population is unknown; most studies are based only on questionnaire survey or structured clinical interview and results range from very low percentages (4%) [32] to frequencies close to 40% [41]. All the comparative studies emphasize the difference in RBD frequencies between the MSA and LBD groups versus the PD group, considering RBD a possible marker of more widespread brainstem pathology. In fact, while RBD is an almost universal sleep finding in MSA, in PD its frequency remains lower, even when only PD patients with sleep disorders are considered [42]. Nevertheless, given the possibility that RBD may have prognostic implications, perhaps predicting a poorer outcome, its recognition is an important target. Acknowledging that a questionnaire could represent the simplest and most useful diagnostic tool to identify RBD in PD cases, Comella et al. [43] assessed the accuracy of the ICSD clinical diagnostic criteria for RBD in PD patients by PSG. They found that the criteria are neither sensitive nor specific in identifying RBD in PD patients. Concerning the lower specificity, disturbed nocturnal sleep and the higher frequency of sleep apnea and other sleep disorders

(i.e. sleep fragmentation, periodic limb movements during sleep, etc.) may represent confounding factors when the diagnosis is only based on clinical interview. The frequency of RBD in 33 consecutive PD patients has recently been explored comparing the ICSD minimal criteria and PSG findings [44]. RBD on PSG was indicated in 33% of the patients, but only 5/9 of these patients met the ICSD clinical criteria, confirming the low sensitivity of the clinical criteria for RBD in PD. Moreover, on PSG 58% of patients displayed RWA, suggesting that a very large population of patients may develop clinical RBD later in the disease course. Most patients in the above study were on antiparkinsonian treatment, and no data are available on the clinical onset of RBD. Nevertheless, this study demonstrated for the first time that RBD is rarer in PD than in MSA and LBD but is not uncommon, suggesting again its potentially prognostic value. Hopefully, large longitudinal PSG studies exploring the frequency of RBD in different carefully studied clinical PD phenotypes may weigh the clinical relevance of this important sleep feature.

6. Conclusions

In humans, the nature of the mechanism producing RBD remains unknown but, as demonstrated in animal models, the involvement of the REM sleep atonia cells of the pons is strongly suggested by symptomatic cases. The different degrees of frequency of RBD in MSA, LBD and PD may mirror different pathological aspects of a unique spectrum of diseases, the so called synucleinopathies. Within the tegmental pontine structures, prominently involved in neuronal degeneration in PD and having strong connections with both the extrapyramidal and the REM sleep systems, the peduncolopontine nucleus (PPN) [45] may represent the bridge between the extrapyramidal and the REM atonia systems (in fact, it displays its main connection with the substantia nigra, but also links with the REM atonia generators) and thus the crucial structure implicated in the impaired motor control of REM sleep [46–48] in synucleinopathies. These syndromes could therefore represent a model disease for human RBD. In fact, the PPN is afflicted by different degrees of neuronal degeneration in synucleinopathies. Whereas MSA is always characterized by an extensive loss of pontine neurons [49–51], a significant reduction of cholinergic neurons and Lewy bodies in the PPN is commonly found in moderate and severe PD [52]. Within PD, the association RBD-PD could represent a specific clinical phenotype underlying pathological subtypes.

Another important point is the possibility that 'idiopathic' RBD arising in older people has a common pathological substrate with synucleinopathies, and may indicate a poor outcome. If clinical studies demonstrate that 'idiopathic' RBD may precede by years, and even decades, the appearance of a Parkinsonian syndrome (mostly MSA or LBD), functional brain imaging studies seem to demonstrate impairment in striatal dopamine transmission in 'idiopathic' RBD [53]. The severity is less than in PD, but significant when compared with controls. Thus, at least in the vast majority of elderly patients, isolated RBD should be considered as a potential clinical sign of a synucleinopathy rather than a benign and easily treatable sleep disorder. Given this possibility, the use of the term 'cryptogenic' RBD, rather than 'idiopathic', seems more appropriate to indicate the strong possibility of an underlying synucleinopathy and the need for detailed follow-up of these patients.

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