# REM Sleep Behavior Disorder Associated with Parkinson's Disease and Multiple System Atrophy

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> *"... In this stage, the sleep becomes much disturbed. The tremulous motion of the limbs occur during sleep, and augment until they awaken the patient, and frequently with much agitation and alarm. ... but even when exhausted nature seizes a small portion of sleep, the motion becomes so violent as not only to shake the bed-hanging, but even the floor and sashes of the room. …".*
>
> (James Parkinson, 1817) [1]

## 5.1 RBD in Parkinson's Disease

In his seminal "Essay on the Shaking Palsy", James Parkinson recognized sleep disturbances as part of the clinical syndrome that was to be later named after him. The observed phenomena possibly represent the first description of REM sleep behavior disorder (RBD) in Parkinson's disease (PD). However, for the larger portion of the ensuing two centuries, medical research focused on motor symptoms and the pathology of the substantia nigra, as this was regarded as the key to understanding the disease and creating successful treatment strategies for alleviating tremor, akinesia and rigidity. Over the last three decades, however, the first evidence of

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idiopathic RBD converting into PD was detected, and RBD was proposed as a precursor to neurodegenerative disease [2]. These findings opened a window into a better understanding of PD pathology. Together with data on the prevalence and clinical impact of sleep problems in PD [3, 4] and reports on sleep-related violence in PD [5, 6], they also kindled a successful new collaboration of movement disorder neurologists and sleep specialists. Sleep disorders and non-restorative sleep are now recognized as part of a non-motor symptoms complex with a significant impact on quality of life in PD patients and their caregivers [7–9]. Moreover, 81% of patients originally diagnosed with idiopathic RBD (iRBD) had developed Parkinsonism and/or dementia approximately 14 years after onset of RBD [10]. Other study groups confirmed these findings of RBD preceding PD by more than a decade, with a neurological disease-free survival rate from time of iRBD diagnosis of 65.2% at 5 years and 7.5% at 14 years [11–13].

Serial presynaptic dopamine transporter scintigraphy (DAT Scan) demonstrated a progressive loss of striatal tracer uptake in patients with iRBD [14]. F-fluorodeoxyglucose positron emission tomography (FDG-PET) metabolic patterns in iRBD were shown to closely resemble those of early PD patients [15]. Consequently, RBD is now recommended as a biomarker in clinical cohorts investigating prodromal PD (for an overview see [16]). Furthermore, iRBD may evolve to multiple system atrophy (MSA) or dementia with Lewy bodies (DLB) and only rarely to Alzheimer's disease or any tauopathy [11–13, 17, 18]. Lewy bodies and Lewy neurites as the histopathological hallmark of PD, multiple system atrophy (MSA) and DLB contain aggregated α-synuclein. Autopsy studies on patients originally diagnosed with iRBD showed evidence of neurodegenerative disease in 170 of 172 cases. An overwhelming majority (94%) of these patients were neuropathologically classified with a synucleinopathy [19], thus linking RBD to the misprocessing of α-synuclein with the appearance of Lewy bodies, although neuropathologically confirmed Lewy bodies may be incidental and not necessarily fully consistent with the clinical picture of a neurodegenerative disorder in an individual subject during his/her lifetime. However, the hypothesis that RBD is one of the most important premorbid markers of neurodegenerative disease with α-synuclein is generated from the long-term follow-up of patients with severe, often violent, RBD. The following overview attempts to compile what we know about the occurrence and clinical relevance of RBD in clinically manifest PD and MSA.

### 5.1.1 The Evolution of RBD in Early PD

Manifestation of motor symptoms such as rigidity, resting tremor, akinesia (often with an asymmetrical presentation) and later on postural instability, together with a positive response to levodopa, defines the diagnosis of PD according to UK Brain Bank criteria [20]. Reduction of facial expression, shuffling gait, reduced arm swing, micrographia and reduced fine motor dexterity are considered further typical signs of the disease. These symptoms relate to the well-established dopamine deficiency that is due to substantial degeneration of dopaminergic neurons in the substantia nigra. Consequently, substitution of the dopamine precursor levodopa will, at least in the early stages of manifest motor disease, lead to an almost complete

restoration of motor function. The continued alleviation of motor symptoms with levodopa and the emergence of fluctuations and dyskinesias are regarded as pathognomonic for the so-called prototypical PD. At the beginning of our millennium, pathoanatomical studies by Braak and collaborators led to the development of a staging system for PD. This is based on the topographical and temporal progression of α-synuclein containing Lewy bodies and neurites from olfactory structures and the medulla rostral to the pons, midbrain and substantia nigra, spreading to limbic structures and lastly the neocortex [21]. This staging model is currently widely accepted because it embraces premotor and prodromal disease features as well as disease progression in later stages, although it may not explain the variety of PD phenotypes.

Data from animal experiments underlines the role of the ventral mesopontine junction (VPM-J) for the control of sleep time and muscle activity during sleep, showing that a lesion in the caudal part of VPM-J leads to motor activity during REM sleep closely resembling that of human RBD [22]. As the VPM-J is located close to the substantia nigra, it has been hypothesized that the progression of RBD to Parkinsonism is related to the spread of damage from the VPM-J to the substantia nigra [22]. At the time of motor manifestations of PD, pathoanatomical Braak stage 3–4 has already been reached. Following what we know about the ascension of Lewy body pathology and the regulation of REM sleep/REM sleep muscle atonia, one would suppose that the overwhelming majority of these newly diagnosed PD patients would present with RBD. However, a recently published meta-analysis on the prevalence of RBD in newly diagnosed PD patients (a total of 2462 patients and 3818 healthy controls in 8 studies) demonstrated an overall mean prevalence of RBD in newly diagnosed PD of 23.6% (range 4.3–69.4%) [23]. The fact that due to assessment methods RBD diagnosis was considered only "probable" in five out of the eight studies included in the meta-analysis may explain the wide range of prevalences given.

The one study using video-polysomnography (vPSG) for RBD assessment identified 25% of a de novo PD patient cohort with RBD [24]. Of note, none of the patients in this cohort were pre-diagnosed with RBD, and results from validated RBD screening instruments showed poor sensitivity and specificity. Another 26% of patients were seen with minor motor behaviors and/or vocalizations that did not meet the diagnostic criteria for RBD or even REM sleep without atonia (RWA) [25]. These phenomena were labelled as REM behavioral events (RBE) and were shown to correspond to dreaming [26]. vPSG follow-up data revealed an increase in the prevalence of RBD to 43% after 2 years; all patients with RBD at baseline continued to show RBD, and 38% of those originally diagnosed with RBE had converted to manifest RBD, leading to the hypothesis that RBE may be prodromal RBD [27].

This concept is supported by preliminary data from an ongoing longitudinal vPSG study from Bologna, where video analysis revealed similar findings of RBE and transition to manifest RBD over time (Provini and Sixel-Döring, in preparation). A similar issue has been described for isolated RWA; electromyographic measures increased over time, and transition to RBD occurred in 7% of otherwise healthy study subjects [28]. As 71% of these subjects also scored positive for at least one marker for impending neurodegenerative disease, such as cognitive impairment, finger speed deficit, impaired colour vision, olfactory dysfunction, orthostatic

hypotension and/or substantia nigra hyperechogenicity, longitudinal cohorts are necessary to establish the role of both prodromal RWA and prodromal RBD.

Although subgroup analysis of motor and cognitive features failed to establish a specific PD phenotype associated with RBD in this cohort of early PD patients [24, 27], another study group presented 3-year follow-up data of de novo PD patients at baseline and identified RBD as a predictor of earlier cognitive decline [29].

### 5.1.2 The Clinical Phenomenology of RBD in PD

Various visual classification systems have attempted to describe and characterize REM sleep-associated dream-enacting behaviors with the aid of the video recordings synchronized to the polysomnography (PSG). Some differentiate between simple and complex movements [30, 31] or rate RBD manifestations as mild, moderate or severe according to the behaviors visible [17]. Others used qualitative descriptions and elaborate electromyographic measurements [32, 33] or detailed video analysis of the number, duration and type of motor events during REM sleep [34]. The REM sleep behavior disorder severity scale (RBDSS) [35] uses phenomenological categories such as the localization of movements—distal, proximal or axial—and the presence or absence of vocalizations (Table 5.1) with the final RBD severity score being determined by the most severe episode observed during one night.

Descriptive video analysis demonstrated that PD patients with RBD mostly show minor/mild motor events during REM sleep, with only 3.6% of all RBD episodes observed being judged as violent [34]. Another study identified violent behaviors in only 15.6% of PD patients with RBD [17]. In a study using the RBDSS [36], 30%

**Table 5.1** REM sleep behavior disorder severity scale (RBDSS) [52]

| Motor events | Vocalizations |
|---|---|
| **0. = no visible motor activity, RWA present**<br>Only definition criteria of RWA according to ICSD are fulfilled, no other phasic muscle activity in the limbs or face is visible or obvious on recording<br>**1. = small movements or jerks**<br>Isolated, single hand or foot movements or facial jerks visible, restricted to the distal extremities and/or face<br>**2. = proximal movements including violent behavior**<br>Single movements or series of movements including proximal extremities, no change of position<br>**3. = axial movements including bed falls**<br>Movements with axial involvement and/or change of body position, falls | **.0 = no vocalization**<br>Snoring with some sound may be present and should be differentiated from REM-associated vocalization<br>**.1 = all sleep-associated sounds other than respiratory noises**<br>Talking, shouting, murmuring, laughing and screaming, either tonic or phasic, are present during at least one REM episode |

*ICSD* International Classification of Sleep Disorders, *RWA* rapid eye movement (REM) sleep without atonia

of PD patients with RBD showed movements involving the trunk and changes of body position with the risk of bed falls and thus fulfilled criteria for violent, potentially harmful behaviors. Thirty-eight percent of the patients showed proximal limb involvement. Another 32% of PD patients were identified with only mild, non-violent manifestations of RBD in the distal extremities or the face. Vocalizations were present in 59% of the patients in the study. Their occurrence increased with RBD severity and was found to be highest in the group of PD patients who had axial involvement. In only 7% of the patients vocalizations were the sole manifestation of RBD during the night investigated. However, a comparative study of PD patients with RBD demonstrated that in 60% of patients investigated with vPSG on consecutive nights, the occurrence as well as the phenomenology of dream-enacting motor events in PD showed a considerable night-to-night variability in the individual patient [35], ranging from mild distal jerks and gestures in one night to thrashing and axial movements with the risk of falling out of bed or hurting the bed partner in the other night. Predictors or risk factors for violent RBD manifestations in PD are currently not known. These aspects need to be considered when counselling on RBD, its implications for nocturnal safety and potential pharmacotherapy. The night-to-night variability also leads to the question of how many nights are needed to definitely diagnose clinical manifestations of RBD in a patient. However, as electromyography (EMG) scores have not been shown to differ on two consecutive nights, one night of PSG may suffice if careful video analysis is combined with EMG criteria [37, 38].

Due to a lack of longitudinal vPSG-supported data, we currently do not have sufficient knowledge about the natural course of RBD severity as PD progresses, i.e. whether late-stage PD patients still continue to exhibit the same amount and phenotype of RBD manifestations as in the early stage of PD. Clinical observations suggest a possible modification of the RBD symptomatology during the course of the disease. In early stages the amount of RWA has been shown to increase over time even in PD patients without RBD [27], as if the ability to produce REM muscle atonia is lost with disease progression. Figures 5.1 and 5.2 depict the polysomnographic changes in RWA from the de novo stage to an advanced stage of PD with RBD; whereas the de novo patient mainly shows phasic EMG activity, the more advanced patient seems to have lost the ability to produce atonia during REM sleep, with continuous tonic EMG activity and additionally superimposed phasic activity.

Another unresolved question concerns the origin of REM-associated motor behaviors. In three studies using video analysis of RBD in PD patients [35, 36, 39], the behavioral patterns observed during RBD episodes showed remarkably restored motor control with fluid, fast, even forceful movements and thus quite in contrast to the slow, often restricted Parkinsonian movement pattern during wakefulness. Speech, however, remained mostly unintelligible. These findings imply a REM sleep-related disjunction of pyramidal and extrapyramidal motor systems where movements during RBD episodes are generated by the motor cortex and follow the pyramidal tract, bypassing the extrapyramidal pathways [39].

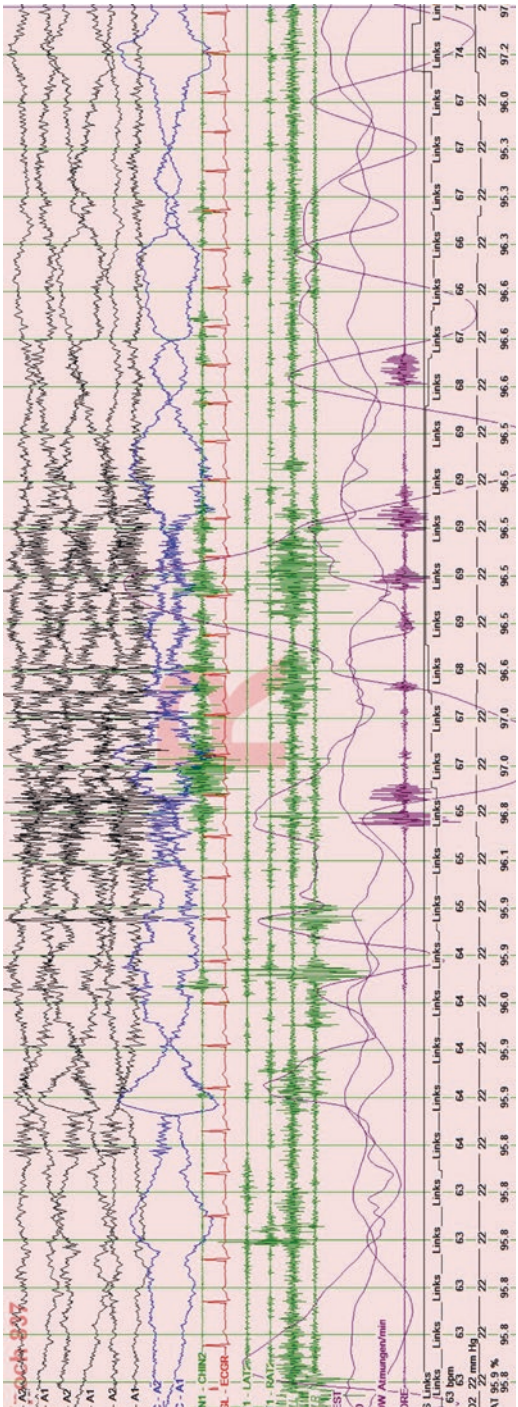

**Fig. 5.1** Polysomnography screenshot showing a REM sleep epoch of a de novo Parkinson's disease patient with REM sleep behavior disorder. EMG sensitivity for chin and both Mm. flexor digitorum superficialis ("Arm L" and "Arm R") set at 5 μV/mm. Time basis set at 1 s/div with 30 s/page. Note excessive amounts of phasic muscle activity in chin and both Mm. flexor digitorum superficialis. Patient is trashing with the arms and talking

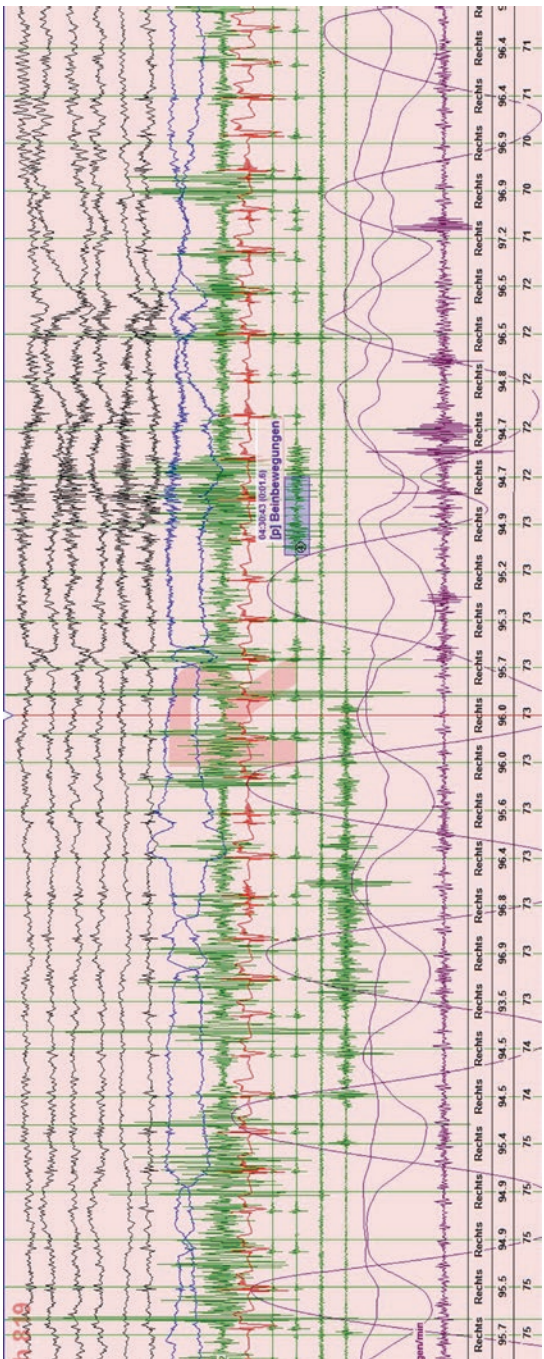


**Fig. 5.2** Polysomnography screenshot showing a REM sleep epoch of an advanced Parkinson's disease patient with REM sleep behavior disorder. EMG sensitivity for chin and both Mm. flexor digitorum superficialis ("Arm L" and "Arm R") set at 5 μV/mm. Time basis set at 1 s/div with 30 s/page. Note excessive amounts of tonic and superimposed phasic muscle activity in chin as well as increased phasic muscle activity in both Mm. flexor digitorum superficialis ("Arm L" and "Arm R"). Patient is mumbling and boxing

### 5.1.3 RBD in Advanced PD

Violent behaviors of RBD in PD can occur at any time during the course of the disease and are not related to either the early or advanced stage of PD. As PD progresses, nocturnal disturbances with abnormal, disruptive and injurious behaviors resulting from RBD, in addition to frequent awakenings due to akinesia or restless legs syndrome, may bother the patient and substantially add to the caregiver's burden. A questionnaire-based study revealed that 15% of consecutive PD patient/caregiver pairs in an outpatient clinic reported the experience of sleep-related injuries, with RBD as a probable cause in 66% of PD patients [5]. PD patients on dopaminergic medication may exhibit a variety of nocturnal motor and non-motor behaviors such as confusional states, hallucinations and/or severe periodic leg movements in sleep (PLMS), which can be mistaken for RBD when relying on patients' history alone. Critical issues on the usefulness of the RBD screening questionnaire (RBDSQ) have not only been raised by the aforementioned study [24] in early PD patients, but RBDSQ validation studies in more advanced PD patients [38, 40] have also raised issues on its usefulness and applicability in patients with a clinically manifest Parkinsonian syndrome, as sensitivity and specificity varied, strongly depending on the clinical context. These findings are in line with recent results from a further study on questionnaire-based RBD detection with the RBDSQ in sleep-disordered non-PD patients and healthy controls [41], calling for a reappraisal and revision.

A predominant feature of RBD consists of an increased amount of vivid dreams, which can often be recalled by the patient [6] and may perhaps prove a more accurate screening tool for RBD. At present, vPSG is mandatory for establishing a definite RBD diagnosis in PD [42, 43], and differentiating RBD from nocturnal hallucinations or confusion is essential for choosing adequate therapy. In the largest cross-sectional cohort of sleep-disturbed PD patients investigated with vPSG so far, the frequency of RBD was determined at 46% [44]. Older age, longer disease duration, a higher Hoehn and Yahr stage, a higher daily dose of levodopa, more falls, more fluctuations and a higher rate of psychiatric comorbidity were identified as associated factors. These findings are in line with other studies [45–48], suggesting that the appearance of RBD during the course of PD may be a predictor of entering a more advanced stage of the disease. In addition, recent cross-sectional studies provided evidence that PD patients with RBD tend to have specific motor and non-motor manifestations such as autonomic dysfunction including orthostatic hypotension, impairment of colour vision [49] and freezing of gait [50].

The aforementioned observations in early PD, pathological and neuroimaging studies and studies on biomarkers and non-motor symptoms align to the clinical phenomenology of PD with a high heterogeneity of early features and later outcomes of the disease. This has led to a recently published new concept proposing three possible routes of spread of pathology in PD, namely, a brainstem route with early sleep dysfunction such as RBD and dysautonomia; an olfactory-to-limbic route with depression, fatigue, central pain and weight loss; and lastly a neocortical subtype with early cognitive symptoms, anxiety, apathy and falls (for an overview see [51]). A recent study using diffusion magnetic resonance imaging (MRI)

connectometry and calculation of quantitative anisotropy showed microstructural white matter changes in the bilateral cingulum pathways, corpus callosum, bilateral inferior fronto-occipital fasciculi, bilateral corticospinal tracts and the middle cerebellar peduncles specific to PD patients with RBD [52, 53]. These findings support the concept of different pathological pathways leading to different phenotypes of PD. If this concept proves true, objective biomarkers will have to be evaluated in future long-term cohorts.

## 5.2 RBD in Multiple System Atrophy (MSA)

MSA presents in two clinical variants, namely, MSA Parkinson type (MSA-P) with a primarily Parkinsonian syndrome and MSA cerebellar type (MSA-C) with predominantly cerebellar symptoms. Similar to PD and DLB, both variants are characterized by the pathological accumulation of α-synuclein in specific brain areas. Whereas in PD and DLB α-synuclein aggregates in neurons, forming the aforementioned Lewy bodies and Lewy neurites, insoluble α-synuclein forms glial cytoplasmic inclusions inside oligodendroglia as a corresponding pathological hallmark of MSA [54]. In the clinical setting, MSA-P in particular may at first present with symptoms very similar to prototypical PD. The sporadic, progressive adult-onset disorder of currently unknown etiopathogenesis is defined by consensus criteria [54], comprising autonomic failure, poor levodopa-responsive Parkinsonism or cerebellar ataxia and/or supporting neuroimaging abnormalities. Rapid disease progression marks MSA as a sort of "fast-track PD" without the benefit of symptomatic dopaminergic therapies to reduce the burden of the disease. The first systematic PSG study in MSA identified RBD in 90% of patients [55]. A more recently published cross-sectional PSG study combined with a meta-analysis of previous studies found a prevalence of RBD of 88% in MSA patients [56]. Both studies conceded that many patients report symptoms of RBD before the onset of motor deficits. In one study 5% of the patients with idiopathic RBD who had converted to neurodegenerative disease within a mean of 5.1 years were clinically classified with MSA [11]. These findings allow for the conclusion that, similar to prototypical PD, RBD may be a premotor manifestation of MSA.

Comparative PSG studies in PD and MSA patients showed no qualitative differences in RBD-related symptoms detected by video or on the PSG recordings [17, 57]. However, patients with MSA had a higher percentage of RWA, a greater index of PLMs and less total sleep time compared to PD patients, suggesting a more severe dysfunction in the structures modulating sleep [17]. Similar to PD, MSA patients also showed a transient disappearance of Parkinsonian motor symptoms with normalization of movement patterns during RBD episodes [58, 59]. However, an attempt to differentiate MSA-P and MSA-C with vPSG and movement analysis failed, showing equally disturbed sleep profiles in both cohorts as a probable indicator of similar pathologic mechanisms [59, 60].

Data from retrospective sleep interviews on the evolution of RBD in MSA suggest that in the majority of patients, RBD occurs prior to, or at the onset of, the motor manifestation of the disease and then disappears, with RBD symptoms remaining

mostly non-violent or even silent [57]. Unfortunately, cohorts of MSA patients followed over several years are not available to document the evolution of RBD over the course of the disease, and longitudinal vPSG-supported data are currently nonexistent. A single case study reported a decreased frequency of elaborate motor behaviors during REM sleep over time, in correlation with predominant tonic chin EMG activity, possibly as a sign of increased rigidity as the disease progressed [58]. In another two cases, the transition of originally idiopathic RBD to MSA with RBD was documented by vPSG, showing a diminished frequency of RBD episodes during the course of the disease accompanied by increasing abnormalities in the patients' sleep with nearly continuous motor and verbal behaviors and rapid oscillations of stage-determining PSG features, consistent with the concept of status dissociatus [61]. These observations support the hypothesis that the severity of the neurodegenerative process is mirrored in the increasing destruction of physiological sleep macrostructure.

In a recently published case series, five of eight patients (63%) with pure autonomic failure (PAF) were identified with RBD [62]. Of note, all patients met strict clinical criteria for PAF by reporting autonomic symptom duration for >5 years (mean 11.2 years) without any sign of motor or cerebellar involvement. In contrast to patients with MSA, dream-enacting behaviors manifested well after the PAF diagnosis, with an average time delay of 7.1 years. These findings suggest that PAF may represent a mild form of CNS α-synucleinopathy, as indicated by autopsy reports of Lewy bodies not only in postganglionic sympathetic neurons but also in the locus coeruleus and substantia nigra [63].

## 5.3 Concluding Remarks

Patients diagnosed with violent RBD in sleep centres have a high risk of converting to manifest neurodegenerative diseases within years or decades, associated with the misprocessing of α-synuclein over time. Presently, it is not possible to predict in patients with RBD whether they will develop prototypical PD, DLB or MSA. In PD, the ascending spread of Lewy body pathology from the REM sleep regulating medullar and pontine centres to the substantia nigra, as described by the Braak staging system, fits with the concept of RBD as a premotor manifestation of the disease and may thus be termed as prodromal PD. When using vPSG for the diagnosis of RBD in accordance with the currently valid diagnostic criteria for RBD as defined by the International Classification of Sleep Disorders, 3rd version, 25% of newly diagnosed PD patients actually show RBD. Recently, RBE, as dream-associated motor behaviors and/or vocalizations prodromal to full-blown RBD, have been described in de novo PD patients. In contrast to iRBD, the clinical manifestation of RBD in PD patients includes mostly mild to moderate motor behaviors. Violent and potentially injurious dream enactments are present in only 15–30% of patients. Although a considerable night-to-night variability of RBD severity in PD has been demonstrated, it is currently not clear whether the dream-enacting features of RBD may eventually disappear in later disease stages, as described for MSA. Clinical features and neurophysiologic measures of RBD do not differ between prototypical PD and MSA or between the two known types of MSA. Although clinical evidence that RBD predicts a specific clinical course of PD is not yet driven by sufficient

longitudinal data, results from large PD cohorts underline the role of RBD as a marker for entering a more advanced stage of the disease.

**Note Added in Proof:** A recently published study merits inclusion, along with its accompanying Editorial: (1) Pagano G, De Micco R, Yousaf T, Wilson H, Chandra A, Politis M. REM behavior disorder predicts motor progression and cognitive decline in Parkinson disease. Neurology 2018 Aug 8; doi: 10.1212/WNL.0000000000006134. (2) Mahowald MW, Schenck CH. The "when" and "where" of α-synucleinopathies: Insights from REM sleep behavior disorder. Neurology. 2018 Aug 8; doi: 10.1212/WNL.0000000000006129.

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