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Morbidities in Rapid Eye Movement Sleep Behaviour Disorders

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Abstract

Idiopathic Rapid Eye Movement (REM) Sleep Behaviour Disorder (iRBD, RBD without any obvious comorbid major neurological disease), is strongly associated with numerous comorbid conditions. The most prominent is that with neurodegenerative disorders, especially synuclein-mediated disorders, above all Parkinson Disease (PD). Idiopathic RBD is an important risk factor for the development of synucleinopathies. Comorbidity studies suggest that iRBD is associated with a number of other potential pre-motor manifestations of synucleinopathies such as, cognitive and olfactory impairment, reduced autonomic function, neuropsychiatric manifestations and sleep complaints. Furthermore, patients with PD and RBD may have worse prognosis in terms of impaired cognitive function and overall morbidity/mortality; in dementia, the presence of RBD is strongly associated with clinical hallmarks and pathological findings of dementia with Lewy bodies. These findings underline the progressive disease process, suggesting involvement of more brain regions in patients with a more advanced disease stage. RBD is also associated with narcolepsy, and it is likely that RBD associated with narcolepsy is a distinct subtype associated with different comorbidities. RBD is also associated with antidepressant medications, autoimmune conditions, and, in rare cases, brainstem lesions.

Keywords

REM Sleep Behavior Disorder; morbidity; narcolepsy; parkinsonism; comorbidity

Rapid Eye Movement (REM) Sleep Behaviour Disorder (RBD) is strongly associated with neurodegenerative disorders, especially synucleinopathies such as, Parkinson Disease (PD), Dementia with Lewy Bodies (DLB), and Multiple System Atrophy (MSA) [1, 2]. A

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significant finding is that 'idiopathic' RBD (iRBD) is a major risk factor for the development of future parkinsonism/dementia [2–4]. The brain stem has been recognized as a central component of the pathophysiology of RBD, particularly REM Sleep without Atonia (RWSA). During the past 15 years, RBD research has intensified due to the condition's strong associations with synucleinopathies, in an effort to understand better the pathogenic basis of these disorders and how this affects brainstem regions important for RWSA [5]. RBD is frequently comorbid with narcolepsy, probably through a different mechanism from that in synucleinopathy [6]. Antidepressant use is also associated with RBD [7]. Less frequently, structural lesions in the pontine region may cause RBD [8, 9]. This paper reviews comorbidities in RBD with and without other major neurological diseases. Narcolepsy has been covered in another review, as has RBD as a predictor of neurodegenerative disease. These topics will be briefly mentioned, and other comorbidities will be discussed.

External causes and medical comorbidities in Parkinson diseases and RBD

PD patients show a number of comorbidities/non-motor symptoms, including cognitive impairment (from mild cognitive impairment to dementia including DLB) [10–12], psychiatric symptoms (hallucinations, psychosis, depression) [11–14], autonomic impairment (attenuated blood and heart rate responses, skin changes, gastrointestinal and urogenital abnormalities) [15–21], sleep problems (sleep fragmentation, macro- and micro-sleep changes, motor and behavioral findings including RBD), daytime fatigue and sleepiness, and impaired smell, among others. Many of these findings are present in RBD, suggesting that they are also prodromal markers of disease. Regardless of the underlying cause, these comorbidities can impair quality of life, and therefore, merit diagnosis and treatment even if neurodegenerative synucleinopathy is not yet manifested.

Risk factors for RBD and PD/DLB overlap. The cause of PD may involve both genetic and environmental factors and is more common in males. Familial aggregation and numerous genes associated with familial and sporadic PD have been identified. A number of lifestyle and environmental risk factors (e.g., exposure to pesticides, heavy metals and other chemicals, such as solvents) and protective factors (e.g. drinking coffee, smoking, uric acid) have been suggested, but a biological basis for these associations have not been established [22]. Studies assessing possible shared etiological components between PD and other diseases show that RBD, constipation, anosmia and, to a lesser degree, depression and anxiety increase PD risk, but the evidence is not conclusive for all these factors. Consistent with the role of idiopathic RBD as a prodromal sign of PD, recent epidemiological studies in idiopathic RBD suggest that many risk factors are similar to PD (pesticide exposure, farming, head injury) and some are similar to dementia (low educational level, head injury). However, the findings also differed in important ways for some exposures –particularly caffeine consumption and smoking, which were not associated with protection against RBD [23]. This suggests that caffeine and smoking may 'protect' against PD either by delaying diagnosis (e.g., symptomatic motor benefit [24], increased alertness) or by functioning as a protective mechanism that specifically targets basal ganglia structures.

Development of synucleinopathies including PD, spans a continuum from non-motor stages to progressive disease evolution, including impaired motor, cognitive, psychiatric, autonomic functioning, developing over years or even decades [25]. Recognized non-motor symptoms and findings include complex symptomatology with impaired olfaction and cognition, psychiatric and autonomic problems, daytime sleepiness/fatigue and sleep-related conditions. Thus, it is likely that non-motor symptoms are strongly correlated.

Cognitive impairment and dementia

A number of studies have addressed comorbid cognitive impairment in RBD. Compared with controls, individuals with idiopathic RBD reveal subtle cognitive impairment in psychometric tests [26–28]. This impairment most closely resembles that of mild DLB, including posterior visuoperceptive changes, memory improvement with cueing, etc. Coexisting RBD and cognitive impairment may be risk factors for later development of PD (and DLB, especially), although this has not yet been established in prospective studies [28]. A number of studies have evaluated other physiological measures of the cognitive changes associated with idiopathic RBD. EEG slowing, a potential marker of dementia, has been found in idiopathic RBD [29], and is also known to be associated with a higher risk of mild cognitive impairment from prospective studies (although a link to dementia itself has not yet been conclusively established) [30]. Changes in cerebral perfusion have been identified in RBD [31]; RBD patients have hypoperfusion in the frontal and parietotemporal regions, as well as hyperperfusion in the pons, putamen and hippocampus. These findings are similar to what is seen in PD. Moreover, in RBD with additional mild cognitive impairment, hippocampal and putamenal hyperperfusion was more pronounced with additional left pericentral gyrus abnormalities, consistent with PD dementia or DLB [32].

Once PD or dementia has been established, detection of RBD may have implications for the evolution and nature of cognitive impairment. In PD patients, coexisting RBD is associated with worse cognitive function than in PD patients without RBD [33, 34]. This appears to be part of a generally 'diffuse' form of PD, and other features associated with PD dementia (akineti-rigid subtype, freezing, autonomic dysfunction, depression and falls) are associated with RBD in PD patients [35]. Furthermore, patients with parkinsonism with associated RBD also showed electroencephalographic slowing in posterior regions, perhaps suggestive of increased dementia risk [29]. When hallucinations were assessed, PD with both hallucinations and RBD, had a significantly greater risk of cognitive impairment and mortality ; whereas, PD patients without RBD and hallucinations showed no progression during a two year follow-up period [11]. In a recent prospective study, the presence of RBD in PD increased risk for later development of dementia [36]. Therefore, in PD patients, the presence of RBD and hallucinations suggests a worse prognosis for progression into PD dementia [30]. Within dementia itself, the identification of RBD is a very strong sign of the presence of DLB as the underlying pathology. Although Alzheimer disease is the most common form of dementia by far, only a single case of autopsy-confirmed Alzheimer dementia has been reported in association with RBD, compared with the numerous DLB cases described [37]. In a recent pathological study of dementia, simply noting the presence of possible RBD was sufficient to enable a more accurate diagnosis of DLB than the use of the complete DLB consensus criteria [38]. Moreover, within autopsy-proven DLB, the presence of RBD was associated with a more classic clinical presentation (i.e., earlier presence of clinical DLB hallmarks) and a 'purer' synuclein pathology [39].

Autonomic dysfunction

A number of studies have identified autonomic dysfunction in RBD. RBD patients show attenuated cardiac autonomic responses. In a study of cardiac rhythm during sleep, the normal heart rate response to limb movement or arousals was attenuated. It was progressively impaired, particularly in PD patients (with or without RBD) and to an intermediate extent in idiopathic RBD patients, but was normal in controls [19]. Similar patterns in autonomic testing during wakefulness have been noted [40]. Further studies with ¹²³I-MIBG scintigraphy, a marker of post-ganglionic cardiac sympathetic denervation, have shown substantial and consistent abnormalities in iRBD [41, 42]. RBD is associated with MSA, but not with Pure Autonomic Failure [43]. This suggests that in patients with iRBD

and RBD-associated synucleinopathy several brain structures are involved beyond the pontine nuclei involved in motor control during REM sleep.

This probably reflects underlying synucleinopathy, since autonomic dysfunction has been identified in PD, DLB and MSA. The cardiac autonomic dysfunction of iRBD is similar in nature to that found in established synucleinopathy [16, 18, 20, 40, 44–48]. Autonomic dysfunction was strongly linked to the presence of RBD in PD [16], suggesting again that RBD may indicate a specific disease subtype.

For patients with iRBD, cardiac autonomic dysfunction can result in clinical symptoms, including orthostatic hypotension, (which may be treated with medications such as fludrocortisone, domperidone, midodrine or physostigmine), and exercise intolerance. It also implies a need for periodic reassessment of indications for hypertensive medications in RBD patients, as they may no longer be needed once a patient has developed idiopathic RBD.

Higher constipation scores have also been noted in idiopathic RBD [44]. Within established PD, constipation was more prevalent in PD patients with RBD than in those without [49], although this has not been found in all studies [3]. . No clear association was found between RBD and symptoms of urinary dysfunction or erectile dysfunction in established PD cases. Despite this obvious correlation, there are no prospective data on the association between urogenital or gastrointestinal function in iRBD and the risk of developing clinical PD, despite the common gastrointestinal and voiding problems found with synucleinopathies. Constipation is readily treatable, and may result in a substantial impairment in quality of life, so vigilance for autonomic problems in patients with idiopathic RBD is warranted.

Motor function

Motor abnormality is the hallmark of RBD. Quantitative electromyographic analysis of idiopathic and parkinsonian RBD indicate the presence of specific abnormalities, including changes in motor tone and phasic activity compared with normal controls [50, 51]. The motor component of dream enactment behavior varies, including minor limb movements, body jerks, and complex behaviors, and violent and non-violent behaviors [52]. Nocturnal movements in RBD are faster and more often repeated, jerky and pseudohallucinatory; they are not self-centered or associated with tremor, and rarely involve the environment in an appropriate manner [53]. These movements are notably different from waking movement in parkinsonism, which is characterized by slowness, rigidity and tremor. These findings suggest that the upper (first neuron) motor stream bypasses the basal ganglia during REM sleep [54].

Beyond the motor abnormalities of sleep, idiopathic RBD patients have numerous subtle motor abnormalities, even before development of established parkinsonism. Transcranial Magnetic Stimulation (TMS) with short latency afferent inhibition (SAI) had weaker responses in RBD patients compared with controls. TMS responses are associated with several neural mechanisms involved in motor responses; however, in the subgroup of RBD who also had cognitive impairment, SAI was correlated with the degree of cognitive impairment, suggesting that RBD affects cholinergic mechanisms, leading to cortical or subcortical dysfunction [55]. Consistent with their elevated risk of parkinsonism, RBD patients exhibit numerous mild motor abnormalities similar in nature to those seen in parkinsonism [56]. These abnormalities first appear to develop approximately four to eight years before parkinsonism is definitively diagnosed and are able to identify prodromal PD reliably approximately two to three years before diagnosis. Although PD patients, especially those with associated RBD [57], have a risk of falls, this has not been evaluated in iRBD patients compared with controls.

Psychiatric diseases and antidepressants

RBD is frequent in psychiatric patients. A recent study from an outpatient psychiatric practice reported that 5.8% of patients had RBD-like behaviors. These were particularly prevalent in patients taking antidepressants, compared with other categories of psychiatric medications [58]. A case-control study including patients with mixed psychiatric disorders with RBD who were compared with RBD patients without concurrent psychiatric diseases found similar behaviors and polysomnographic results in the two groups [59]. However, the study did not determine whether RBD is associated with specific subtypes of psychiatric disease or its causal relation. RBD was also highly prevalent in a case study of a population of veterans with post-traumatic stress disorder [60], but its relationship with comorbid conditions and diseases was not evaluated.

The association between psychiatric disease and RBD is confounded by antidepressant medications, which have also been reported to be strongly associated with RBD. Tricyclic antidepressants and serotonin reuptake inhibitors, in particular, have been implicated in RSWA and RBD [61]. The medications associated with RBD have been exhaustively reviewed elsewhere in this supplement. It is possible that antidepressants unmask latent RBD rather than cause it: in a study in which medications were modified, RBD symptoms improved, but the RSWA persisted [58].

Currently, studies that address treatment and long-term prognosis in antidepressant-associated or depression-associated RBD are lacking. There could be numerous relationships between depression/antidepressants and RBD. If antidepressants trigger a pure 'pharmacological' RBD unassociated with synuclein degeneration, the risk of developing synucleinopathy is presumably low. On the other hand, if depression is another prodromal risk factor for PD, it could be associated with a higher risk of disease. In one recent study, the presence of psychiatric illness in idiopathic RBD predicted an increased risk of developing Parkinson disease [62]. It is worth noting that only 9/21 patients with psychiatric illness in this study were taking antidepressants, implying that the study may have been measuring prodromal 'depressive PD' rather than antidepressant-associated RBD. Preliminary results from the Montreal cohort could not confirm that depression was associated with a higher risk of developing disease; in fact, the trend was in the opposite direction (Postuma et al., submitted). In this study, patients with idiopathic RBD taking antidepressants had a lower risk of developing neurodegenerative disease, although other prodromal markers of neurodegeneration were nonetheless clearly present. This suggests that antidepressants may trigger an earlier clinical presentation of RBD that, nevertheless, is still due to an underlying synucleinopathy.

Other sleep problems

Apart from abnormal motor manifestations of REM sleep, other sleep problems are generally not prominent in idiopathic RBD. A study evaluated cyclic alternating pattern and found an increased CAP rate in RBD patients, suggesting that not only REM sleep but also NREM sleep were affected in RBD patients [63]. In general, most studies do not reveal major abnormalities of the stages, efficiency or latency of sleep, etc. This is somewhat surprising, given the common abnormalities of these stages in established disease. There have been some preliminary suggestions that patients with poor sleep latency and a lower proportion of slow-wave sleep may have a higher risk of developing dementia [64]. RBD patients may have a higher prevalence of sleepiness as measured on the Epworth Sleepiness scale, although differences were relatively modest compared with controls [28]. No systematic assessments of insomnia or restless legs syndrome have been published, despite their association with PD. Finally, special mention of obstructive sleep apnea must be made.

There are clear descriptions of patients with a history of RBD who had obstructive sleep apnea on polysomnography. In these cases, episodes of dream-enactment were time-locked to apneic episodes, perhaps suggesting that confusional arousals were responsible for the behavior. This implies that a firm diagnosis of RBD cannot be made in the presence of sleep apnea, unless symptoms persist after successful treatment with appropriately placed CPAP.

Structural pontine lesions

From the initial description [65] of RBD, the nocturnal behaviors of RBD have been compared to oneiric behaviors in cats with bilateral locus coeruleus lesions [66]. A likely hypothesis is the involvement of the sublaterodorsal nucleus, which actively inhibits spinal motor tone during REM sleep [37]. In the majority of cases of RBD there is probably a functional lesion in the brainstem that causes analogous symptoms, while in a small number of reported cases, a structural lesion in the brainstem can be identified as the cause of RBD. Multiple sclerosis is the most commonly reported cause, and in one case RBD preceded a full clinical manifestation of multiple sclerosis [67, 68]. In a review of 135 consecutive MS cases, four had symptoms of RBD [69]. There are additional reports of inflammatory brainstem lesions causing RBD [70, 71]. RBD has been reported in cases with medullary and pontine strokes [72, 73]. Rare and other causes of structural pontine lesions causing RBD include tumor and cavernoma [74].

Other neurodegenerative diseases

RBD has been described in a wide range of other neurodegenerative diseases. These include Machado–Joseph disease, other spinocerebellar ataxias, Huntington’s chorea, progressive supranuclear palsy, corticobasal degeneration, Guadeloupean parkinsonism, and RBD in a family with pallidopontonigral degeneration [75–80] [81–83]. In most of these conditions, RBD appears to be less prevalent than in synucleinopathies. Nevertheless, this suggests that RBD is not specific to synucleinopathy. The common association between synucleinopathy and RBD may reflect the typical anatomic progression pattern of neurodegeneration in these disorders. It is striking that no prospective sleep center study has ever reported any of these diseases emerging from idiopathic RBD. Although in part, this is very likely ;given the relative rarity of such disorders, it may also suggest that the brainstem regions responsible degenerate later in non-synuclein neurodegenerative diseases.

Narcolepsy and autoimmune diseases

There is a strong correlation between RBD and narcolepsy with cataplexy, compared with narcolepsy without cataplexy, idiopathic hypersomnia and controls [84–87], and it is even stronger when RBD occurs early in life [84]. Further analysis shows that the association is largely explained by hypocretin deficiency, suggesting that RBD occurs as a consequence of a functional defect in pontine neurons innervated by hypocretinergeric projections [6]. This implies that RBD in narcolepsy may have a different etiopathogenesis from that causing idiopathic RBD. This has been supported by findings that RBD in narcolepsy is not associated with the changes in dream content reported in idiopathic RBD, and a tendency for movements to be less severe. Unlike idiopathic RBD, narcolepsy is associated with a profound derangement of all sleep stages, including sleep state stability. It is not clear whether REM atonia loss in narcolepsy may sometimes be due to micro-intrusions of other sleep stages (or micro-arousals) into REM sleep.

Narcoleptic patients with RBD have a reduced heart-rate response to periodic leg movements [88], but it is not known whether this is related to hypocretin deficiency or to another mechanism. While increased rates of depression [89], obesity [90, 91], and pain

modulation [92] have been identified in narcolepsy, especially narcolepsy with cataplexy, we do not yet know whether concomitant RBD modulates these associations.

Although the pathogenesis of narcolepsy has not been established, increasing evidence points to a potential autoimmune cause. There are indications that other autoimmune diseases may also be associated with RBD. There have been cases of encephalitis secondary to voltage-gated potassium channel antibody and anti-Ma antibody associated with RBD [93]. In these cases, no evident brainstem lesions were present. Although microscopic brainstem lesions cannot be ruled out, potential roles of hypocretin deficiency or limbic lesions may also have contributed to dream enactment in these cases. Transient RBD, improving as the disease resolves, has also been associated with Guillain–Barre Syndrome, particularly in patients experiencing autonomic dysfunction and hallucinations [80]. The authors suggested that a coincident autoimmune hypocretin deficiency could contribute to these cases. Finally, a high prevalence of associated autoimmune disease was reported, particularly in female patients with young-onset RBD, whereby 8/40 (20%) women (7/20 (35%) of whom were under 50 years of age), reported an autoimmune disease compared with 0/75 men.

Conclusions

Comorbidities in RBD include synucleinopathies and their associated symptoms, narcolepsy, antidepressant usage, and pontine injury/dysfunction. Even in iRBD, there are subtle symptoms of synucleinopathy, such as decreased cognitive ability, olfactory impairment, reduced autonomic function, depression and daytime sleepiness. Many of these are treatable, so vigilance is warranted. In addition, patients with PD and RBD may have worse prognosis in terms of cognitive function and increased morbidity/mortality. Narcolepsy is a common comorbidity, particularly in younger RBD patients, but it is not currently known whether RBD occurring in narcolepsy has any specific prognostic significance. Psychiatric disease is associated with RBD, although this association may be mediated by antidepressant use. RBD can also occur secondarily to injury to pontine structures or to those brain regions providing input to pontine structures, neurodegenerative diseases other than synucleinopathies, and in selected autoimmune conditions.

Future research should clearly assess comorbid conditions in RBD, particularly those that pertain to the risk of developing neurodegenerative diseases, and aim to understand the pathophysiological processes, and the possibility of disease modification.

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