Sleep Medicine 14 (2013) 782–787

Contents lists available at SciVerse ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Morbidities in rapid eye movement sleep behavior disorder ☆

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ARTICLE INFO

Article history:
Available online 29 January 2013

Keywords:
REM Sleep Behavior Disorder
Morbidity
Narcolepsy
Parkinsonism
Comorbidity
Neurodegenerative disorder

ABSTRACT

Idiopathic rapid eye movement (REM) sleep behavior 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.

1. Introduction

Rapid eye movement (REM) sleep behavior 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 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 (RSWA). 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 RSWA [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.

2. 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

☆ Author contributions: Poul Jennum is the main author, Ron Postuma, Yo-El Ju, Geert Mayer commented on the manuscript.

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http://dx.doi.org/10.1016/j.sleep.2012.11.002

treatment even if neurodegenerative synucleinopathy is not yet manifested.

2.1. 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.

3. 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 putaminal 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 (akinetic-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 as 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].

4. 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