Clinical Biomarkers of Neurodegeneration in REM Sleep Behavior Disorder

Junying Zhou¹,², Jihui Zhang¹, Siu Ping Lam¹, Xiangdong Tang², Yun Kwok Wing¹

¹Department of Psychiatry, The Chinese University of Hong Kong, Shatin, Hong Kong SAR
²Sleep Medicine Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Rapid eye movement sleep behavior disorder (RBD) is currently considered as a prodromal stage of α-synucleinopathies neurodegeneration. The update data suggested that over 80% patients with idiopathic RBD eventually developed neurodegenerative disease after a mean of 14 years interval from the onset of RBD. A series of potential biomarkers have been identified to predict the development of neurodegeneration in idiopathic RBD, including olfactory loss, color vision deficit, depression, mild cognitive impairment, excessive daytime sleepiness, dopamine dysfunction, and tonic electromyographic activity. Early recognition of the predictive markers of neurodegeneration in idiopathic RBD is essential for development of intervention or prevention strategies at the presymptomatic stage. Nonetheless, the current literature is lacking biomarkers that might reflect the α-synuclein neuropathology at the earliest stages. Future studies with large samples and systematic follow-up are needed to confirm more potential markers of neurodegeneration at its early stages.

Key Words: REM sleep behavior disorder, Neurodegeneration, Biomarkers, Parkinson's disease.

Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by loss of muscle atonia and abnormal dream-enactment behaviors during REM sleep.¹ The most important feature of RBD is its risk of developing neurodegenerative disease, especially α-synucleinopathies, such as Parkinson disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA).² ³ A recent follow-up study reported that over 80% patients with idiopathic RBD eventually developed neurodegenerative disease after a mean of 14-year interval from the onset of RBD.⁴ In other words, RBD is widely recognized as an early stage of the neurodegeneration.

Since patients with RBD are at a substantial risk of developing neurodegenerative diseases, this prodromal period represents a window of opportunity to intervene the underlying neurodegenerative process which will have a major impact from a public health perspective. Thus, it is essential to look for the relevant biomarkers that might predict the evolution of neurodegeneration in idiopathic RBD. Up to now, some studies have identified that RBD was associated with a myriad of clinical manifestations [e.g., olfactory loss, color vision deficit, autonomic dysfunction, psychiatric disorder, mild cognitive impairment (MCI), and personality changes].⁵ ⁶ This review will summarize whether these features could serve as the potential predictive markers of neurodegeneration in idiopathic RBD.

Risk of Neurodegenerative Diseases in Idiopathic RBD

In 1996, Schenck et al. firstly reported the potential association between RBD and neurodegenerative disease.⁷ They found that 11 (38%) patients initially diagnosed as idiopathic RBD developed a parkinsonian disorder at a mean interval of 13 years after the onset of RBD. In 2013, the longitudinal data had updated their report that up to 81% of patients with idiopathic RBD would eventually convert into parkinsonism/dementia.⁸ In the past decade, this finding has been confirmed by other research groups. Iranzo et al. retrospectively assessed...
44 idiopathic RBD patients and reported that 45% of patients developed neurodegenerative disease after a mean of 12 years from the onset of RBD. They diagnosed 9 patients with PD, 6 DLB, 1 MSA, and 4 MCI by regular follow-up with detailed clinical history and neurological examination. In a cohort study with 93 RBD patients, Postuma et al. quantified the long-term risk of neurodegeneration. The estimated risk of neurodegenerative disease in patients with RBD was 17.7% at 5-years, 40.6% at 10-years, and 52.4% at 12 years. Our group also investigated the evolution of RBD towards neurodegenerative disorders in 91 patients with idiopathic RBD with a mean follow-up of 5.6 years. We found the 5-year and 9-year risk of neurodegeneration was 8.5% and 38%, respectively. The relatively lower estimation may be partly related to the strict criteria for parkinsonism diagnosis, instead of the onset of symptoms as reported by patients. All these studies consistently indicate that idiopathic RBD is a prodromal symptom of neurodegenerative disease.

**Potential Predictive Biomarkers in Idiopathic RBD**

The diagnosis of PD usually depends on the classic clinical symptoms and signs, such as resting tremor, rigidity and bradykinesia. However, more than 50% of substantia nigra dopamine neurons will have been lost when the motor signs first appear. Thus, it is essential to identify the potential predictive biomarkers of RBD.

**Olfactory loss**

Olfactory loss is the most prevalent non-motor symptoms in the early stage of PD. More than 95% of patients with PD ultimately present with olfactory dysfunction. In a community-based cohort study, impaired olfaction was associated with a 5.2-fold increased risk of developing PD. Therefore, olfactory loss has been vastly considered as a reliable marker for the prediction of PD. In 2006, Fantini et al. reported that 61% of RBD patients versus 16% controls showed abnormal olfactory function. In 2009, Postuma et al. reported that patients with idiopathic RBD had substantial olfactory loss compared with controls, but less impairment than that of PD. A recent longitudinal data determined the predictive value of olfactory dysfunction for neurodegeneration in idiopathic RBD over a 5-year follow up, in which the diagnostic accuracy of olfactory test was over 80%. The authors suggested that the assessment of olfactory function, particularly odor identification may predict the early transition to α-synuclein-mediated neurodegenerative disease in idiopathic RBD.

**Autonomic dysfunction**

Autonomic dysfunction is common in PD, which affects more than 70% of patients. Symptoms of dysautonomia are variable, which include sexual dysfunction, bowel and bladder abnormalities, cardiovascular symptoms, gastrointestinal disorders, and sleep disturbances. The deposition of synuclein in PD was found in both the central and peripheral autonomic nervous systems, including the hypothalamus, the dorsal motor nucleus of the vagus, and postganglionic sympathetic tissues. Furthermore, Braak staging system suggested that the peripheral autonomic ganglia was involved in the pathologic stage 1 of PD. In other words, some specific autonomic symptoms may be the early manifestation of PD. There are strong evidences for the occurrence of a series of autonomic abnormalities (e.g., constipation, urinary and sexual dysfunction, orthostatic hypotension) preceding the motor symptoms of PD. Thus, these autonomic dysfunctions have been suggested as reliable biomarkers that may predict the development of PD.

According to Braak staging, the pathology of pontine areas (stage 2) could result in RBD. The peripheral autonomic neuronal loss may occur before pontine involvement, and therefore, the autonomic dysfunction was expected to precede the onset of RBD. In recent years, autonomic symptoms including constipation, erectile dysfunction, urinary dysfunction, and orthostatic hypotension were similarly found in patients with RBD. Besides, cardiac activation during sleep was abnormal and a reduced cardiac uptake of metaiodobenzylguanidine (a marker of sympathetic heart innervation) has been found in patients with idiopathic RBD. It is unclear whether autonomic dysfunction can predict neurodegeneration. In a cohort study, the significant reduction in RR-standard deviation was found in patients with idiopathic RBD compared with controls. However, there were no differences in patients who did or did not develop neurodegenerative disease. Recently, a prospective study suggested that the autonomic dysfunction was not associated with eventual risk of development of neurodegenerative disease. Thus, the utility of autonomic dysfunction as a potential predictor of neurodegeneration in RBD remains unclear.

**Color vision deficit**

The abnormality of color vision is one of the non-motor features in patients with PD, which may reflect decreased dopamine levels in amacrine and retinal cells. The Farnsworth-Munsell 100-Hue test is the common tool to assess visual dysfunction in many studies of PD. Color vision impairment is also common in RBD, which suggests that abnormal vision may be found at the earliest stage of neurodegeneration. Recently, in a 10-year prospective cohort, color vision deficit in-
increased a 3.1-fold risk of neurodegenerative disease conversion in idiopathic RBD. This finding indicates that color vision might help to predict neurodegeneration as a prodromal marker in RBD.

**Cognitive impairment**

Cognitive impairment is common in PD. Even at the early disease stage, 34% of PD patients were reported to have MCI. A population-based cohort found that PD patients had an almost 6-fold increased risk of developing dementia compared to healthy controls. Furthermore, studies have indicated that MCI is a risk factor for dementia in PD, specifically, executive and visuospatial dysfunctions predicted later onset of dementia in PD patients. Therefore, it is essential to recognize the cognitive changes in early-stage of PD, which may predict the dementia process. Cross-sectional studies have shown that idiopathic RBD was associated with the cognitive impairments, especially verbal memory, executive function and visuospatial ability. These cognitive impairments in idiopathic RBD are similar to the pattern of cognitive changes observed at the early stage of PD and DLB. In this regard, several longitudinal follow-up studies have demonstrated that neuropsychological deficits at baseline, such as visuospatial learning, attention and executive functions, had worsening over time in RBD patients compared with controls. Molano et al. found idiopathic RBD patients with MCI might be more at risk of developing a neurodegenerative dementia than those with normal cognitive function. Recently, a retrospective follow-up study confirmed the poorer performances in general cognitive function, executive function and visuospatial abilities in idiopathic RBD as reported in prior studies. In this study, the progressive cognitive decline was associated with disease duration, and lower executive function at baseline increased the conversion risk. In another cohort study, there was no clear evidence that baseline MCI could predict clinical PD, but it predicted conversion to dementia. Overall, most studies have indicated that cognitive impairment might be a biomarker of neurodegeneration in RBD.

**Excessive daytime sleepiness**

Excessive daytime sleepiness (EDS) is a common non-motor symptom of PD, affecting up to 50% of patients. A longitudinal study revealed an increase of EDS prevalence from 4.1% at baseline to 40.8% after 8 years in PD patients who never used dopaminergic drugs. Recently, another study replicated this finding that EDS increased in parallel with disease progression in a cohort of PD patients. Therefore, the development of EDS in PD is considered as part of the pathology related to the degeneration of the lower brainstem involving in sleep-wake regulation. One epidemiological study reported that there was more than a threefold excess risk for developing PD in elderly men with EDS from the general population. This finding suggests that EDS could serve as a preclinical marker of PD and supports the assumption that the disease pathology itself contributes to EDS.

To date, few studies in relation to sleepiness in RBD have been reported and little is known about the predictive role of EDS developing neurodegenerative disease in patients with idiopathic RBD. A recent study reported that sleepiness was associated with idiopathic RBD and predicted more rapid conversion to parkinsonism and dementia. However, this study is limited by the relatively small sample size and short follow-up periods.

The progressive neuronal loss in the arousal system including the locus coeruleus, the pedunculopontine nucleus, the basal forebrain, the median raphe, and the hypothalamus, which may contribute to impaired alertness in early PD. Since the neurodegenerative process in PD spreads from lower brainstem areas to the midbrain, this explains the prevalence of EDS increases as the disease progresses. It is suggested that the pathophysiology of RBD is the dysfunction of brainstem nuclei that regulate REM sleep. In line with the hypothesis, some structural lesions of the brainstem were detected by various neuroimaging technologies, which suggested the brainstem involvement in REM-sleep regulation in patients with RBD. These findings suggested that the abnormalities in the arousal system were associated with the genesis of EDS in RBD. In other words, the pathogenesis of EDS could be a prodromal symptom of neurodegeneration in idiopathic RBD.

**Psychiatric disorders**

Parkinson disease is commonly associated with psychiatric disorders including depression, anxiety, psychotic symptoms and impulse control disorder (ICD). These psychiatric manifestations (particularly depression) may precede motor symptoms of PD by several years. The prevalence of depression in PD is approximately 40%, which has been suggested as an important preclinical marker of PD. In a large multicenter cohort study, patients with depression were investigated at an increased risk (odds ratios 2.2) of developing PD in the later life. In line with the finding in PD, there is reliable evidence to suggest that depression could increase the risk of neurodegeneration in RBD. Our group demonstrated that patients with a history of depression at baseline were at higher risk of developing neurodegeneration over a long-term follow-up. Recently, we further found that a reduced striatal presynaptic dopamine transmission in patients with depression comorbid with RBD, but not in those with depression only. In this regard, our finding could potentially suggest an early neuro-
degeneration process of RBD among patients with depression, and indicate that depression may be a prodromal marker of neurodegenerative disease in RBD.

There are increasing evidences that PD patients have ICDs, including compulsive or pathological gambling, buying, sexual, and eating. ICD has been mostly reported to be associated with the usage of dopamine agonists, but they were also found in patients not taking dopamine agonists in PD. Growing evidences indicate that PD patients with RBD have more severe motor and non-motor symptoms than those without RBD, reflecting that RBD would be associated with a more widespread degenerative process. Interestingly, a recent study also demonstrated that PD patients with possible RBD have a higher risk of manifesting ICD symptoms compared to those without RBD. This study suggested that PD patients with RBD would have more severe alterations in mesocorticolimbic dopaminergic pathway, which plays a key role in impulse control regulation, when compared to those without RBD. Nonetheless, the occurrence of ICD in idiopathic RBD has not been reported, and whether these impulsive problems would be involved in the underlying pathological process of neurodegeneration is still unclear.

Personality changes
Studies suggest that PD is associated with certain personality traits. Some traits such as anxiety proneness, introversion, low novelty seeking, cautiousness and rigidity have been suggested to precede PD onset. Moreover, neuroticism and introversion are associated with an increased risk of PD. In line with the finding in PD, a case-control study found that the personality changes in RBD, presented as having increased harm avoidance and a trend towards reduced novelty seeking compared with controls. However, a prospective follow-up study showed that baseline personality variables could not clearly predict the risk of neurodegeneration in idiopathic RBD. The authors speculated that PD personality could be lifelong, present equally in idiopathic RBD and established PD. Thus, the predictive value of personality changes is unclear, more prospective studies will be required to elucidate the role of personality characteristics in predicting risk of neurodegeneration in idiopathic RBD.

Dopamine dysfunction
The crucial pathological feature of PD is the neurodegeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc). However, when the classical motor symptoms of PD appear, there would already have been substantial loss (more than 50%) of dopaminergic neurons in SNpc. Imaging of dopaminergic neurons with [123I]β-CIT single photon emission computed tomography (SPECT) or fluorodopa F-18 positron emission tomography (PET) are in-vivo ways to visualize and quantify the degree of dopaminergic lesion in PD. Numerous studies with PET or SPECT have consistently observed the dopaminergic nigrostriatal dysfunction with a reduction of fluorodopa F-18 uptake or downregulation of dopamine transporter (DAT) expression in PD. Dopaminergic nigrostriatal impairment has also been clearly described in idiopathic RBD. These findings demonstrate that dopamine cell loss in substantia nigra occurs not only in patients with Parkinsonism, but also in RBD. Moreover, a recent study found that nigra-caudate dopaminergic functioning impairment was related to the presence of RBD, both in its idiopathic form and in PD patients. In 2010, Iranzo et al. showed that 75% of idiopathic RBD patients with reduced binding of DAT at baseline developed synucleinopathy, and those with normal neuroimaging remained disease-free. Therefore, dopamine dysfunction may be a sensitive marker to identify neurodegeneration in RBD. These imaging techniques provide objective means for the early detection and quantification of dopaminergic degeneration and for monitoring disease progression in RBD.

Excessive EMG activity
The loss of muscle atonia during REM sleep is the pathognomonic characteristic of RBD, which is manifested as increased tonic and phasic electromyographic (EMG) activity in polysomnography. It is thought that excessive EMG activity in RBD reflects dysfunction of the brainstem structures modulating REM sleep atonia. Furthermore, excessive tonic and phasic EMG activity during REM sleep were found to increase over time in patients with idiopathic RBD. This finding suggests that there is an underlying progressive pathologic process in the brainstem structures, which is consistent with the increased risk for developing neurodegenerative disease in RBD. Another longitudinal study observed that patients with idiopathic RBD who developed neurodegenerative disease were found to have increased chin EMG activity, but not phasic activity. Thus, the severity of tonic EMG activity may predict the development of PD. The authors speculated that tonic EMG activity reflecting the degeneration of sublaterodorsal nucleus which is more closely linked the pathogenesis of PD. In 2003, Eisensehr et al. have similarly found that muscle activity during REM sleep was associated with reduction of striatal DATs in RBD. The neuroimaging finding demonstrated that increased muscle activity during REM sleep was correlated with the reduced striatal DATs reflecting dopamine cell loss in the substantia nigra. Therefore, loss of REM atonia particularly tonic EMG activity could be a predictor of neurodegeneration in RBD.
The Temporal Sequence of Biomarkers for Neurodegeneration in RBD

Although numerous studies have reported a series of potential predictive markers of PD, the relationship between the onset of premotor and motor features is limited. Recently, a study has reported the temporal relationship of these premotor symptoms with that of emergence of a clinical diagnosis of PD. For example, apathy, memory complaints and inattention occurred during the 2-year premotor period, while smell loss, mood disturbances, taste loss, fatigue and pain occurred about 2- to 10-year prior to the diagnosis. Constipation, dream-enacting behavior, EDS and postprandial fullness were frequently observed more than 10 years before the onset of motor symptoms in PD. Postuma et al. reported olfaction and color vision were abnormality in RBD at least 5 years before neurodegenerative disease onset. Nonetheless, the temporal sequence of prodromal markers relative to the occurrence of RBD is not well established. Early recognition of neurodegeneration biomarkers may possibly develop treatment strategies to delay or prevent the process of neurodegeneration. Hence, future studies should be conducted to identify the temporal sequence and predictive value of biomarkers for neurodegeneration in RBD.

Conclusions

REM sleep behavior disorder is a well-established precursor of neurodegenerative synucleinopathy. It provides a window of golden opportunity to intervene the early neurodegenerative process. A series of prodromal biomarkers have the potential to predict the development of neurodegeneration in idiopathic RBD. However, there is a lack of the biomarkers that could detect the α-synuclein pathology at the earliest stage. In future, prospective studies with larger samples of RBD patients would identify more potential predictive markers, including some of the biochemical biomarkers being involved in the pathophysiological process of neurodegeneration.

Acknowledgments

This research was supported by the General Research Fund (Reference number 476610) of the Research Grants Council and the Health and Medical Research Fund (Reference number 01120326) of the Food and Health Bureau of Hong Kong SAR, China, and the National Natural Science Foundation of China (81328010). Dr. Junying Zhou is partly supported by the Faculty Postdoctoral Fellowship Scheme of the Chinese University of Hong Kong.

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