ORIGINAL ARTICLE

Excessive Daytime Sleepiness Predicts Neurodegeneration in Idiopathic REM Sleep Behavior Disorder

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Study Objectives: To determine the association of excessive daytime sleepiness (EDS) with the conversion of neurodegenerative diseases in patients with idiopathic REM sleep behavior disorder (iRBD).

Methods: A total of 179 patients with iRBD (79.1% males, mean age = 66.3 ± 9.8 years) were consecutively recruited. Forty-five patients with Epworth Sleepiness Scale score ≥14 were defined as having EDS. Demographic, clinical, and polysomnographic data were compared between iRBD patients with and without EDS. The risk of developing neurodegenerative diseases was examined using Cox proportional hazards model.

Results: After a mean follow-up of 5.8 years (SD = 4.3 years), 50 (27.9%) patients developed neurodegenerative diseases. There was a significantly higher proportion of conversion in patients with EDS compared to those without EDS (42.2 % vs. 23.1%, p = .01). EDS significantly predicted an increased risk of developing neurodegenerative diseases (adjusted hazard ratios [HR] = 2.56, 95% confidence interval [CI] 1.37 to 4.77) after adjusting for age, sex, body mass index, current depression, obstructive sleep apnea, and periodic limb movements during sleep. Further analyses demonstrated that EDS predicted the conversion of Parkinson's disease (PD) (adjusted HR = 3.55, 95% CI 1.59 to 7.89) but not dementia (adjusted HR = 1.48, 95% CI 0.44 to 4.97).

Conclusions: EDS is associated with an increased risk of developing neurodegenerative diseases, especially PD, in patients with iRBD. Our findings suggest that EDS is a potential clinical biomarker of α-synucleinopathies in iRBD.

Keywords: REM sleep behavior disorder, excessive daytime sleepiness, neurodegenerative disease, Parkinson's disease, dementia.

Statement of Significance

Idiopathic rapid eye movement sleep behavior disorder (iRBD) is regarded as a prodromal stage of synucleinopathies. Early recognition of the potential biomarkers of neurodegeneration in iRBD is essential for the development of intervention strategies at the presymptomatic stage. The current study evaluated whether excessive daytime sleepiness (EDS) could predict the development of neurodegeneration in iRBD. The findings demonstrated that EDS is associated with an increased risk of developing Parkinson's disease in patients with iRBD. Thus, EDS may deem to be a robust clinical biomarker of synucleinopathies related neurodegeneration in iRBD.

INTRODUCTION

Excessive daytime sleepiness (EDS) is one of the most common nonmotor symptoms of Parkinson's disease (PD), affecting up to 50% of patients with PD.[1] The etiology of daytime sleepiness in PD is multifactorial, but the most relevant cause might be the disease itself.[2] A longitudinal study in patients with PD has revealed a progressive increase in prevalence of EDS from 4.1% at baseline to 40.8% after 8 years of follow-up,[3] which indicated that EDS increases with disease progression in PD.[4] Thus, the development of EDS in PD is considered as a part of the integral pathology related to the degeneration of the lower brain stem involving in sleep–wake regulation.[5,6] On the other hand, previous epidemiological study has suggested that EDS was associated with a 3-fold risk of future development of PD in the general population,[7] which suggested that EDS might serve as a preclinical marker of PD.

Rapid eye movement (REM) sleep behavior disorder (RBD) is considered as a prodromal marker of α-synucleinopathies.[8–11] In particular, it is known as the preclinical manifestation of PD according to Braak staging hypothesis.[12] Lately, Movement Disorder Society (MDS) has proposed a set of the research criteria for prodromal PD, which specified RBD as the most predictive prodromal marker with the highest likelihood ratio.[13] Thus, there is increasing attention on searching the biomarkers that might predict the progression of RBD toward PD, such as olfactory loss,[14,15] color vision deficit,[16] depression,[17] and mild cognitive impairment.[18] In addition, a recent study suggested that presence of EDS in iRBD would predict a more rapid conversion to parkinsonism and dementia,[19] albeit this study was limited by a modest sample size and a relatively short follow-up period.

In the current study, we aimed to examine the potential role of EDS in the prediction of increased risk of developing neurodegenerative diseases using an iRBD cohort with a considerable sample size and follow-up period.

METHODS

Study Participants

Eligible iRBD patients in this study were recruited from a cohort of Hong Kong Chinese RBD patients. Please refer to our related paper of this cohort for details.[20] In brief, a total of 179 patients with a diagnosis of iRBD were consecutively recruited from a regional university-affiliated sleep clinic in Hong Kong from January 1997 to October 2014. The diagnosis of RBD, as defined by *International Classification of Sleep Disorders, 2nd edition* (ICSD-2),[21] included (1) a history of motor activity during sleep associated with vivid dream or abnormal REM sleep behaviors occurring during polysomnography (PSG) recording and (2) a loss of REM-related muscle atonia. Exclusion criteria were (1) a concurrent diagnosis of narcolepsy,[22] (2) RBD

symptoms related to antidepressants or related to psychiatric disorders,[9,23] (3) neurodegenerative diseases diagnosed at the time of RBD diagnosis, and (4) pseudo-RBD occurring in patients with obstructive sleep apnea (OSA).[24]

The medical records of all the recruited patients from the date of RBD diagnosis to the censoring date (January 28, 2015) were systematically reviewed in the computerized Clinical Management System (CMS) in Hong Kong.[20] The CMS is an electronic health-care database that provides an integrated, longitudinal, lifelong view of a patient's clinical history. This system is operated within the public hospitals under the Hospital Authority of Hong Kong, which covers over 95% of the health-care provision in Hong Kong. The study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee.

Baseline Evaluation

Demography and Clinical Records

Demographic characteristics including age of onset, age of diagnosis, sex, education level, and body mass index (BMI) were collected at baseline. Comorbid diseases and medication history were reviewed and retrieved from the CMS. Prescription of drugs during the preceding month of PSG diagnosis was recorded. Sleep medication was classified as hypnotic drugs (benzodiazepine, zolpidem, zopiclone, and melatonin), antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitor, and others) and antipsychotic agents. Life time diagnosis of depression was recorded according to the clinical chart.

Questionnaires

Epworth Sleepiness Scale (ESS) was used to assess subjective daytime sleepiness. EDS was defined as ESS ≥ 14, which has a moderate to high correlation with objective sleepiness as determined by multiple sleep latency test (MSLT) in Chinese patients.[25] Smoking and consumption of coffee and alcohol with the frequency of more than 3 times a week were assessed by a structured questionnaire. Current depressive symptoms were assessed by the Chinese version of Beck Depression Inventory (BDI),[23] and current depression was defined as a BDI score > 14. Insomnia was defined according to the presence of self-reported insomnia symptoms of at least 3 times per week.

Polysomnography

All recruited patients underwent at least 1 overnight video-PSG (v-PSG) assessment. The recording of PSG included standard electroencephalogram (C4-A1, O2-A1, C3-A2, with added F4-M1 since 2007), electro-oculogram (LE-A2, RE-A1), submentalis and bilateral anterior tibialis electromyogram (EMG), and electrocardiogram. Other measurements included nasal–oral flow, thoracic and abdominal respiratory efforts, oxygen saturation, breathing sound, and body position. Sleep stages and associated events were manually scored in 30-second epochs according to Rechtschaffen and Kales criteria with the modifications to allow for the persistence of EMG tone during epochs that were otherwise clearly REM sleep.[26] OSA was defined as apnea–hypopnea index (AHI) > 15 events per hour. All patients with OSA were treated with continuous positive airway pressure on the second night in order to exclude possible OSA cases mimicking the presentation of RBD.[27] Periodic limb movements during sleep (PLMS) was defined as periodic limb movement index (PLMI) > 15 events per hour. Video was recorded simultaneously with the PSG to document the motor activity.

Follow-Up Visit

All RBD patients were followed up within the public health-care system in Hong Kong, and the majority of them (96.5%) visited the specialist clinic within a year from the last visit to the censoring date. During the follow-up period, diagnoses of the parkinsonism and dementia syndromes were ascertained by the specialists (e.g., neurologists, psychiatrists, and geriatricians) with reference to the standard diagnostic criteria of PD,[28] multiple system atrophy (MSA),[29] dementia with Lewy Bodies (DLB),[30] and Alzheimer's disease (AD).[31] Duration of definite RBD was calculated from the date of PSG-confirmed diagnosis to January 28, 2015, (censor date) or the date of diagnosis of neurodegenerative diseases.[20]

Statistical Analysis

All statistical analyses were performed using SPSS Statistics version 20.0 (Chicago, IL). For the comparisons between the groups, the nonparametric Mann–Whitney *U* test was used to compare continuous variables. Categorical variables were compared using chi-square or Fisher exact test where appropriate. Cox proportional hazard models were used to calculate the hazard ratios (HR) and 95% confidence intervals (CIs) of developing neurodegenerative diseases between iRBD patients with and without EDS after adjusting for baseline age, sex, BMI, depression (BDI > 14), OSA, and PLMS. Kaplan–Meier curves were also used to compare the survival of developing overall neurodegenerative diseases, PD, and dementia between iRBD patients with and without EDS. A p value of <.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

In this study, 45 (25.1%) iRBD patients with EDS (ESS ≥ 14) and 134 patients without EDS were recruited at baseline. Comparisons of baseline demographic and clinical characteristics and conversion to neurodegenerative diseases during follow-up between patients with and without EDS are presented in Table 1. There were no significant differences in age at onset and diagnosis of RBD, sex, and follow-up duration between the groups. Similarly, no differences were found in lifestyle factors including coffee, alcohol and smoking consumption, sleep medications, comorbid insomnia symptoms, and lifetime depression between patients with or without EDS. However, patients with EDS had a slightly lower education level, higher BMI, and a higher prevalence of current depression.

After a mean follow-up of 5.8 years (range: 0.2–18.3 years), 50 (27.9%) patients with iRBD at baseline developed neurodegenerative diseases. Of the 50 patients, 27 were diagnosed with idiopathic PD, 21 were diagnosed with dementia (7 DLB and 14 probable AD), and 2 were diagnosed with MSA. The median time of conversion to neurodegenerative diseases was 9 years (mean 10.6 years) from RBD onset and 3.1 years (mean 4.3 years) from RBD diagnosis. There was a significantly higher proportion of development of neurodegenerative diseases

Table 1—Demographic and clinical characteristics of idiopathic RBD with and without excessive daytime sleepiness.

	All RBD patients (*n* = 179)	RBD without EDS (*n* =134)	RBD with EDS (*n* = 45)	p
Age at PSG, years	66.3 ± 9.8	66.4 ± 9.9	65.8 ± 9.6	.49
Sex, M/F	144/35	106/28	38/7	.44
Age at onset, years	60.5 ± 13.3	60.8 ± 14.1	59.9 ± 11.0	.31
Follow-up duration, years	5.8 ± 4.3	5.8 ± 4.4	5.5 ± 4.1	.71
≤ Primary education[a], n (%)	74 (46.3)	50 (41.7)	24 (60.0)	.04
BMI, kg/m^2	24.5 ± 5.0	24.1 ± 5.4	25.6 ± 3.4	.003
Coffee (≥ 3 times/week)[a], n (%)	20 (12.6)	16 (13.2)	4 (10.5)	.79
Alcohol (≥ 3 times/week)[a], n (%)	9 (5.7)	7 (5.8)	2 (5.3)	1.00
Smoking (≥ 3 times/week)[a], n (%)	21 (13.2)	19 (15.7)	2 (5.3)	.17
Sleep medication use, n (%)	62 (34.6)	45 (33.6)	17 (37.8)	.61
Antidepressants, n (%)	21 (11.7)	16 (11.9)	5 (11.1)	.88
Hypnotic drugs, n (%)	52 (29.1)	37 (27.6)	15 (33.3)	.47
Antipsychotics, n (%)	4 (2.2)	4 (2.9)	0	.57
ESS	8.9 ± 5.5	6.4 ± 3.6	16.3 ± 2.5	.000
Lifetime depression, n (%)	36 (20.1)	25 (18.7)	11 (24.4)	.40
Current depression (BDI >14), n (%)	10 (5.6)	5 (3.8)	5 (11.1)	.07
Insomnia, n (%)	24 (15.1)	17 (14.0)	7 (18.4)	.51
Developed neurodegenerative disease	50 (27.9)	31 (23.1)	19 (42.2)	.01
PD, n (%)	27 (15.1)	14 (10.4)	13 (28.9)	.003
Dementia (AD + DLB), n (%)	21 (11.7)	16 (11.9)	5 (11.1)	.88
MSA, n (%)	2 (1.1)	1 (0.7)	1 (2.2)	.44

Abbreviations: AD, Alzheimer's disease; BDI, Beck depression inventory; BMI, body mass index; DLB, Dementia with Lewy Bodies; ESS, Epworth sleepiness scale; EDS, excessive daytime sleepiness; MSA, Multiple system atrophy; PD, Parkinson's disease; RBD, rapid eye movement sleep behavior disorder.
[a] *N* < 179 because of missing data.

in iRBD patients with EDS compared to those without EDS (42.2% vs. 23.1%, p < .05), particularly related to the conversion into PD (28.9% vs. 10.4%, p < .01). Nonetheless, the conversion rates for dementia (11.1% vs. 11.9%, p = .88) and MSA (2.2% vs. 0.7%, p = .44) were similar between these 2 groups.

Sleep Variables

The comparisons of baseline PSG variables between RBD patients with and without EDS are shown in Table 2. RBD patients with EDS had a significantly increased mean PLMI (20.3 ± 24.5 vs. 15.3 ± 30.3, p = .04) and a higher rate of PLMS (42.2% vs. 26.9%, p = .04) than those without EDS. In addition, a slightly nonsignificant increased proportion of OSA (AHI > 15/h) was found in patients with EDS (51.1% vs. 35.1%, p = .056). There were no significant differences in total sleep time, sleep latency, sleep efficiency, arousal index, wake after sleep onset, percentage of sleep stages (N1-3 and REM sleep), and AHI between the groups.

Risk of Neurodegenerative Diseases

In an unadjusted Cox regression model, the risk of developing neurodegenerative diseases was increased in RBD patients with EDS (HR, 1.92; 95% CI, 1.08 to 3.41; p < .05) versus those without EDS. The risk was further enhanced for RBD patients with EDS in the final model after adjusting for potential confounding variables, including age at diagnosis, sex, BMI, depression, OSA, and PLMS (HR, 2.56; 95% CI, 1.37 to 4.77; p < .01; Model 2 in Table 3). Similarly, the risk of developing PD was higher in RBD patients with EDS after adjustment of confounding factors (HR, 3.55; 95% CI, 1.59 to 7.89; Table 3). However, there was no higher risk of dementia development in patients with EDS (HR, 1.48; 95% CI, 0.44 to 4.97; Table 3). Notably, there were similar results of the risk of conversion to neurodegenerative diseases in iRBD patients when using the starting point from the time of RBD onset (Supplemental Table 1). The Kaplan-Meier survival curves similarly show that RBD patients with EDS were at an increased risk of developing neurodegenerative diseases, particularly PD but not dementia (Figure 1). When EDS was defined at lower cutoffs of ESS (> 8 or 10), the regression models showed a similar prediction of EDS toward the development of PD, albeit with lower HRs (Supplemental Table 2).

DISCUSSION

This study suggested that EDS is associated with a 2.56-fold higher risk of developing overall neurodegenerative diseases and 3.55-fold higher risk of developing PD respectively. The conversion

Table 2—Sleep parameters of idiopathic RBD with and without excessive daytime sleepiness.

	All RBD patients (*n* = 179)	RBD without EDS (*n* = 134)	RBD with EDS (*n* = 45)	p
Total sleep time, min	338.6 ± 76.7	336.0 ± 78.6	346.5 ± 70.9	.38
Sleep efficiency, %	70.1 ± 13.9	69.4 ± 14.5	72.1 ± 11.9	.41
Sleep latency, min	25.1 ± 26.1	25.9 ± 25.0	22.6 ± 29.3	.13
REM sleep latency, min	129.9 ± 79.5	132.0 ± 80.6	123.4 ± 76.8	.60
Stage 1, %	16.8 ± 8.9	16.8 ± 8.9	16.7 ± 8.7	.95
Stage 2, %	63.0 ± 13.9	62.3 ± 10.0	65.0 ± 22.0	.66
Stage 3, %	2.0 ± 4.1	2.2 ± 4.4	1.4 ± 3.0	.30
Stage REM, %	18.6 ± 8.6	18.5 ± 8.2	18.9 ± 9.9	1.00
WASO, min	118.7 ± 62.4	120.4 ± 67.1	111.2 ± 45.5	.81
Arousal index, /h	18.3 ± 13.5	17.2 ± 12.5	21.3 ± 15.6	.13
AHI, /h	20.1 ± 20.8	18.9 ± 20.4	23.4 ± 22.0	.26
OSA (AHI >15/h), n (%)	70 (39.1)	47 (35.1)	23 (51.1)	.056
PLMI, /h	16.3 ± 28.9	15.3 ± 30.3	20.3 ± 24.5	.04
PLMI in NREM, /h	17.2 ± 29.4	15.2 ± 29.4	23.4 ± 29.1	.03
PLMI in REM, /h	5.9 ± 20.8	6.7 ± 23.4	3.8 ± 8.2	.92
PLMS (PLMI >15/h), n (%)	55 (30.7)	36 (26.9)	19 (42.2)	.04

Abbreviations: AHI, apnea hypopnea index; EDS, excessive daytime sleepiness; NREM, non-rapid eye movement; OSA, obstructive sleep apnea; PLMI, periodic limb movement index; PLMS, periodic limb movements during sleep; REM, rapid eye movement; WASO, wake after sleep onset.

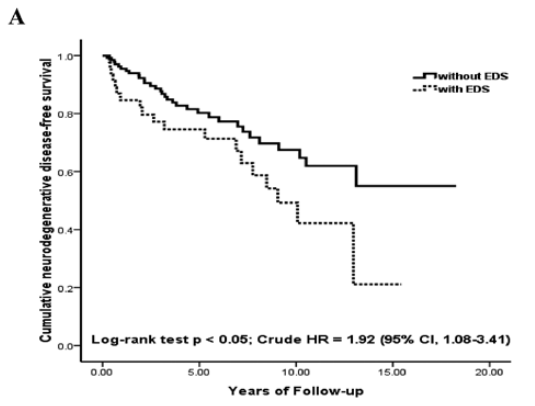
Table 3—Hazard ratios of developing neurodegenerative diseases in idiopathic RBD patients with sleepiness[a].

	Unadjusted		Model 1		Model 2	
	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI
Overall neurodegenerative diseases	1.92[b]	1.08 to 3.41	2.02[b]	1.13 to 3.59	2.56[c]	1.37 to 4.77
PD	2.89[c]	1.36 to 6.16	3.14[c]	1.46 to 6.74	3.55[c]	1.59 to 7.89
Dementia	1.14	0.42 to 3.13	1.18	0.43 to 3.23	1.48	0.44 to 4.97

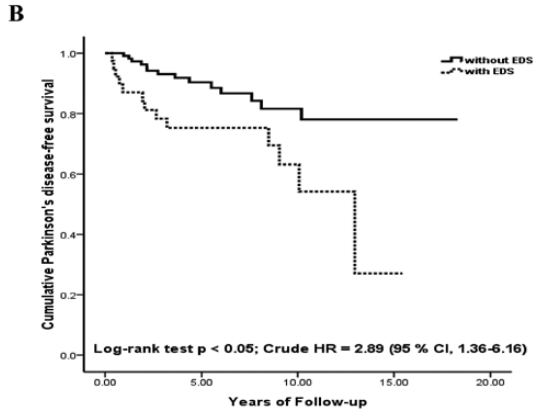
Abbreviations: CI, confidence interval; PD, Parkinson's disease; RBD, rapid eye movement sleep behavior disorder.
[a]Model 1: adjusted for age at PSG, sex. Model 2: adjusted for age at PSG, sex, BMI, depression (BDI > 14), OSA, and PLMS.
[b]$p < .05$.
[c]$p < .01$.

time to neurodegenerative diseases was calculated from the RBD diagnosis in the Cox proportional hazard analysis. Apparently, the time of RBD diagnosis was more precise, whereas the time of RBD onset might be more important for calculating the course of RBD. In the current study, we found a similar result when using the conversion time from the RBD onset. The prevalence of EDS (25%) in patients with iRBD in our study is generally consistent with that of previous report (20%).[19] Although we used a higher cutoff of ESS (>14), we had similar findings with the other study which used a lower ESS cutoff at 10[19]. In addition, our sensitivity analysis with lower cutoffs of ESS (at 8 and 10, respectively) also similarly predicted the risk of future neurodegeneration, albeit with lower risk ratios. As the local ESS cutoff of moderate sleepiness at 14 has a rather high correlation with MSLT,[25] the use of this cutoff may be more applicable to the local population.

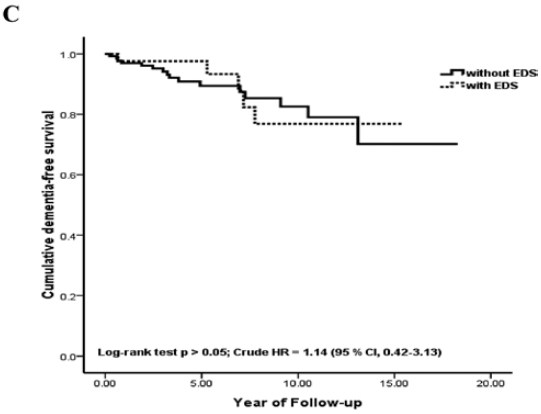
Although multiple factors could account for EDS in the elderly population including nocturnal sleep disruption (such as insomnia, sleep apnea, restless legs syndromes, and PLMS), circadian factors, obesity, depression, and sedative medication,[32–34] our findings remained significant even after adjustment of these potential confounding factors. Arnulf et al. reported that there was no association between sleepiness and those factors such as sex, obesity, nocturnal sleep, and sedative drugs that were commonly seen in patients with iRBD.[19] Similarly, the severity of sleepiness was not correlated with nocturnal sleep abnormalities,[2,35–37] motor problems, cognitive impairment, and dopaminergic medications in previous studies of PD.[2] In other words, the nature of EDS in RBD is likely related to the underlying disease pathology affecting arousal system.[38] It has been suggested that PLMS may reflect a brain stem dysfunction in RBD, which is possibly a potential biological



No. at risk				
Without EDS	134	113	106	103
With EDS	45	34	28	26



No. at risk				
Without EDS	134	125	121	120
With EDS	45	36	34	32



No. at risk				
Without EDS	134	123	120	118
With EDS	45	44	40	40

Figure 1—Cumulative survival of developing (A) overall neurodegenerative diseases, (B) PD, and (C) dementia for idiopathic RBD patients with and without sleepiness. Number of patients at risk of developing neurodegenerative diseases at the beginning of each year is shown below the horizontal axis. EDS indicates excessive daytime sleepiness; PD, Parkinson's disease; RBD, rapid eye movement sleep behavior disorder.

marker of dopaminergic mechanism involved in the pathophysiology of PD.[39,40] Thus, the association of PLMS and EDS in our study further implied the close relationship between daytime sleepiness and the underlying neurodegenerative pathology of RBD. In this regard, our recent finding also suggested that PLMS was an independent predictor of mortality in patients with iRBD.[20]

The progressive neuronal loss in the arousal system including locus coeruleus, pedunculopontine nucleus, basal forebrain, raphe nucleus, and hypothalamus might contribute to impaired alertness in early PD.[5,41] The underlying neurodegenerative process in PD, spreading from the lower brainstem areas to the midbrain,[42] is in parallel to the progressive increase in the reported prevalence of EDS in PD patients upon the disease progression.[43,44] In line with this hypothesis, the structural lesions of the brain stem involved in REM-sleep regulation in patients with RBD were detected by various neuroimaging technologies.[45–48] Interestingly, a recent large case–control study demonstrated no difference in the prevalence of EDS in early untreated PD compared to healthy controls.[49] The study, however, showed a higher rate of RBD in PD with EDS than those without EDS. Similarly, a higher level of sleepiness was seen in PD patients with probable RBD than those without increased sleepiness.[50] These findings suggest that the presence of RBD might be associated with greater sleepiness in PD, which might reflect a more diffuse disease process with more brain stem nuclei involvement in the evolution of RBD into PD.[50]

These structural changes in brain consequently resulted in abnormalities of dopaminergic and nondopaminergic neurotransmitters, such as noradrenaline, acetylcholine, serotonin, and orexin.[44] Dopamine is generally considered as a wake-promoting neurotransmitter.[51] A neuroimaging study showed that ESS score was inversely correlated with dopaminergic transporter binding in the striatum in PD, which suggested that daytime sleepiness was possibly associated with nigrostriatal dopaminergic degeneration.[52] Besides, the loss of orexin neurons in hypothalamus which is correlated with PD progression may also contribute to daytime sleepiness.[53,54] Recently, the impairment of melatonin secretion has been found in PD patients with EDS, which indicated that circadian dysfunction might also underlie certain facet of sleepiness in PD.[55] Thus, further studies should determine the roles of dopamine, orexin, and melatonin in the mechanisms underlying EDS in RBD.

Daytime sleepiness is also a commonly reported sleep problem in patients with dementia, including both DLB and AD.[56] Several cohort studies have found an association between EDS and dementia.[57] Other studies also reported that the development of EDS was correlated with dementia in PD.[58] However, we did not find an association of EDS with dementia in our iRBD patients. There are some possible reasons for the inconsistent results. First, the follow-up period (mean 5.8 years) may not be long enough to observe the occurrence of dementia.[42,59] Second, mild cognitive impairment was not systematically assessed in our cohort, so the early dementia stage could potentially have been missed. Finally, the conversion of RBD towards different types of dementia, such as probable AD, might need further exploration.[60] Although daytime sleepiness has been reported to be more common in patients with DLB than those with AD, we did not analyze the association between EDS and subtypes of dementia due to the small sample size of dementia.

In this regard, further prospective studies with a larger sample size, longer follow-up period, and timely, periodic assessments are warranted to determine the association of EDS with dementia and its subtypes in iRBD.

The strengths of the present study included a considerable sample size, a low dropout rate, and the inclusion of both clinical and PSG variables. In addition, potential confounding factors, including lifestyle factors, sleep medication, nocturnal sleep disorders, depression, OSA, and PLMS, which might contribute to EDS, have been taken into consideration in the analysis. However, this was a retrospective cohort study, and several limitations should be noted in the current study. First, EDS was subjectively measured by ESS and was not assessed by the objective measures, such as MSLT and Maintenance of Wakefulness Test. Although ESS has been shown to have a significant correlation with the objective tests in PD patients,[61] there has been inconsistent report.[62] Nevertheless, ESS is recommended for the evaluation of EDS in patients with PD by the MDS.[13] Second, the diagnosis of neurodegenerative diseases was based on the clinical assessment which might result in some diagnostic assessment problems, especially for dementia. In consistent with other RBD studies, the clinical diagnostic criteria of DLB might not be sensitive enough to differentiate between possible DLB and other types of dementia such as probable AD. Third, the censor date was not the exact time of last specialist assessment which might potentially result in an underestimation of the neurodegenerative diseases in RBD patients. Fourth, this finding only demonstrated that EDS at baseline could be a potential marker for the development of neurodegenerative diseases, but how EDS progresses over time in RBD patients remains unclear.

CONCLUSIONS

Our study found that EDS is associated with an increased risk of developing neurodegenerative diseases, especially PD, in patients with iRBD. These results may suggest that EDS could be a robust clinical biomarker of synucleinopathies related neurodegeneration in iRBD. Further study on the neurochemical and neural circuitry underlying EDS in RBD is needed.

REFERENCES

1. Hobson DE, Lang AE, Martin WR, Razmy A, Rivest J, Fleming J. Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: a survey by the Canadian Movement Disorders Group. JAMA. 2002; 287(4): 455–463.
2. Arnulf I, Konofal E, Merino-Andreu M, et al. Parkinson's disease and sleepiness: an integral part of PD. Neurology. 2002; 58(7): 1019–1024.
3. Gjerstad MD, Alves G, Wentzel-Larsen T, Aarsland D, Larsen JP. Excessive daytime sleepiness in Parkinson disease: is it the drugs or the disease? Neurology. 2006; 67(5): 853–858.
4. Tholfsen LK, Larsen JP, Schulz J, Tysnes OB, Gjerstad MD. Development of excessive daytime sleepiness in early Parkinson disease. Neurology. 2015; 85(2): 162–168.
5. Iranzo A. Parkinson's disease and sleepiness. Sleep Med Clin. 2006; 1:127–137.
6. Diederich NJ, McIntyre DJ. Sleep disorders in Parkinson's disease: many causes, few therapeutic options. J Neurol Sci. 2012; 314(1–2): 12–19.
7. Abbott RD, Ross GW, White LR, et al. Excessive daytime sleepiness and subsequent development of Parkinson disease. Neurology. 2005; 65(9): 1442–1446.
8. Iranzo A, Santamaria J, Tolosa E. Idiopathic rapid eye movement sleep behaviour disorder: diagnosis, management, and the need for neuroprotective interventions. Lancet Neurol. 2016; 15(4): 405–419.
9. Wing YK, Lam SP, Zhang J, et al. Reduced striatal dopamine transmission in REM sleep behavior disorder comorbid with depression. Neurology. 2015; 84(5): 516–522.
10. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. Sleep Med. 2013; 14(8): 744–748.
11. Zhou J, Zhang J, Du L, et al. Characteristics of early- and late-onset rapid eye movement sleep behavior disorder in China: a case-control study. Sleep Med. 2014; 15(6): 654–660.
12. Boeve BF, Silber MH, Saper CB, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. Brain. 2007; 130(Pt 11): 2770–2788.
13. Berg D, Postuma RB, Adler CH, et al. MDS research criteria for prodromal Parkinson's disease. Mov Disord. 2015; 30(12): 1600–1611.
14. Fantini ML, Postuma RB, Montplaisir J, Ferini-Strambi L. Olfactory deficit in idiopathic rapid eye movements sleep behavior disorder. Brain Res Bull. 2006; 70(4–6): 386–390.
15. Mahlknecht P, Iranzo A, Högl B, et al.; Sleep Innsbruck Barcelona Group. Olfactory dysfunction predicts early transition to a Lewy body disease in idiopathic RBD. Neurology. 2015; 84(7): 654–658.
16. Postuma RB, Gagnon JF, Bertrand JA, Génier Marchand D, Montplaisir JY. Parkinson risk in idiopathic REM sleep behavior disorder: preparing for neuroprotective trials. Neurology. 2015; 84(11): 1104–1113.
17. Wing YK, Li SX, Mok V, et al. Prospective outcome of rapid eye movement sleep behaviour disorder: psychiatric disorders as a potential early marker of Parkinson's disease. J Neurol Neurosurg Psychiatry. 2012; 83(4): 470–472.
18. Molano J, Boeve B, Ferman T, et al. Mild cognitive impairment associated with limbic and neocortical Lewy body disease: a clinicopathological study. Brain. 2010; 133(Pt 2): 540–556.
19. Arnulf I, Neutel D, Herlin B, et al. Sleepiness in Idiopathic REM Sleep Behavior Disorder and Parkinson Disease. Sleep. 2015; 38(10): 1529–1535.
20. Zhou J, Zhang J, Lam SP, et al. Mortality and Its Risk Factors in Patients with Rapid Eye Movement Sleep Behavior Disorder. Sleep. 2016; 39(8): 1543–1550.
21. American Academy of Sleep Medicine. *International Classification of Sleep Disorders. Diagnostic and Coding Manual*. Westchester, IL: American Academy of Sleep Medicine; 2005.
22. Knudsen S, Gammeltoft S, Jennum PJ. Rapid eye movement sleep behaviour disorder in patients with narcolepsy is associated with hypocretin-1 deficiency. Brain. 2010; 133(Pt 2): 568–579.
23. Lam SP, Li SX, Chan JW, et al. Does rapid eye movement sleep behavior disorder exist in psychiatric populations? A clinical and polysomnographic case-control study. Sleep Med. 2013; 14(8): 788–794.
24. Iranzo A, Santamaría J. Severe obstructive sleep apnea/hypopnea mimicking REM sleep behavior disorder. Sleep. 2005; 28(2): 203–206.
25. Fong SY, Ho CK, Wing YK. Comparing MSLT and ESS in the measurement of excessive daytime sleepiness in obstructive sleep apnoea syndrome. J Psychosom Res. 2005; 58(1): 55–60.
26. Zhang J, Lam SP, Ho CK, et al. Diagnosis of REM sleep behavior disorder by video-polysomnographic study: is one night enough? Sleep. 2008; 31(8): 1179–1185.
27. Huang J, Zhang J, Lam SP, et al. Amelioration of obstructive sleep apnea in REM sleep behavior disorder: implications for the neuromuscular control of OSA. Sleep. 2011; 34(7): 909–915.
28. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry. 1992; 55(3): 181–184.
29. Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology. 2008; 71(9): 670–676.
30. McKeith IG, Dickson DW, Lowe J, et al.; Consortium on DLB. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology. 2005; 65(12): 1863–1872.
31. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984; 34(7): 939–944.

32. Foley DJ, Vitiello MV, Bliwise DL, Ancoli-Israel S, Monjan AA, Walsh JK. Frequent napping is associated with excessive daytime sleepiness, depression, pain, and nocturia in older adults: findings from the National Sleep Foundation '2003 Sleep in America' Poll. Am J Geriatr Psychiatry. 2007; 15(4): 344–350.
33. Tsuno N, Jaussent I, Dauvilliers Y, Touchon J, Ritchie K, Besset A. Determinants of excessive daytime sleepiness in a French community-dwelling elderly population. J Sleep Res. 2007; 16(4): 364–371.
34. Högl B, Poewe W. [Excessive daytime sleepiness: etiology, differential diagnosis and diagnostic procedures]. Wien Klin Wochenschr. 2001; 113(7-8): 278–284.
35. Razmy A, Lang AE, Shapiro CM. Predictors of impaired daytime sleep and wakefulness in patients with Parkinson disease treated with older (ergot) vs newer (nonergot) dopamine agonists. Arch Neurol. 2004; 61(1): 97–102.
36. Rye DB, Bliwise DL, Dihenia B, Gurecki P. FAST TRACK: daytime sleepiness in Parkinson's disease. J Sleep Res. 2000; 9(1): 63–69.
37. Cochen De Cock V, Abouda M, Leu S, et al. Is obstructive sleep apnea a problem in Parkinson's disease? Sleep Med. 2010; 11(3):247–252.
38. De Keyser J, Ebinger G, Vauquelin G. Evidence for a widespread dopaminergic innervation of the human cerebral neocortex. Neurosci Lett. 1989; 104(3): 281–285.
39. Sasai T, Inoue Y, Matsuura M. Clinical significance of periodic leg movements during sleep in rapid eye movement sleep behavior disorder. J Neurol. 2011; 258(11): 1971–1978.
40. Montplaisir J, Nicolas A, Godbout R. Restless legs syndrome and periodic limb movement disorder. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. Philadelphia: W.B. Saunders; 2000:742–752.
41. Arnulf I, Leu-Semenescu S. Sleepiness in Parkinson's disease. Parkinsonism Relat Disord. 2009; 15 Suppl 3: S101–S104.
42. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003; 24(2): 197–211.
43. Ondo WG, Dat Vuong K, Khan H, Atassi F, Kwak C, Jankovic J. Daytime sleepiness and other sleep disorders in Parkinson's disease. Neurology. 2001; 57(8): 1392–1396.
44. Braak H, Ghebremedhin E, Rüb U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res. 2004; 318(1): 121–134.
45. Unger MM, Belke M, Menzler K, et al. Diffusion tensor imaging in idiopathic REM sleep behavior disorder reveals microstructural changes in the brainstem, substantia nigra, olfactory region, and other brain regions. Sleep. 2010; 33(6): 767–773.
46. Scherfler C, Frauscher B, Schocke M, et al.; SINBAR (Sleep Innsbruck Barcelona) Group. White and gray matter abnormalities in idiopathic rapid eye movement sleep behavior disorder: a diffusion-tensor imaging and voxel-based morphometry study. Ann Neurol. 2011; 69(2): 400–407.
47. Shirakawa S, Takeuchi N, Uchimura N, et al. Study of image findings in rapid eye movement sleep behavioural disorder. Psychiatry Clin Neurosci. 2002; 56(3): 291–292.
48. Mazza S, Soucy JP, Gravel P, et al. Assessing whole brain perfusion changes in patients with REM sleep behavior disorder. Neurology. 2006; 67(9): 1618–1622.
49. Simuni T, Caspell-Garcia C, Coffey C, et al.; PPMI Sleep Working group on behalf of the PPMI Investigators. Correlates of excessive daytime sleepiness in de novo Parkinson's disease: A case control study. Mov Disord. 2015; 30(10): 1371–1381.
50. Rolinski M, Szewczyk-Krolikowski K, Tomlinson PR, et al. REM sleep behaviour disorder is associated with worse quality of life and other non-motor features in early Parkinson's disease. J Neurol Neurosurg Psychiatry. 2014; 85(5): 560–566.
51. Rothman SM, Mattson MP. Sleep disturbances in Alzheimer's and Parkinson's diseases. Neuromolecular Med. 2012; 14(3): 194–204.
52. Happe S, Baier PC, Helmschmied K, Meller J, Tatsch K, Paulus W. Association of daytime sleepiness with nigrostriatal dopaminergic degeneration in early Parkinson's disease. J Neurol. 2007; 254(8): 1037–1043.
53. Fronczek R, Overeem S, Lee SY, et al. Hypocretin (orexin) loss in Parkinson's disease. Brain. 2007; 130(Pt 6): 1577–1585.
54. Thannickal TC, Lai YY, Siegel JM. Hypocretin (orexin) cell loss in Parkinson's disease. Brain. 2007; 130(Pt 6): 1586–1595.
55. Videnovic A, Noble C, Reid KJ, et al. Circadian melatonin rhythm and excessive daytime sleepiness in Parkinson disease. JAMA Neurol. 2014; 71(4): 463–469.
56. Ferman TJ, Smith GE, Dickson DW, et al. Abnormal daytime sleepiness in dementia with Lewy bodies compared to Alzheimer's disease using the Multiple Sleep Latency Test. Alzheimers Res Ther. 2014; 6(9): 76.
57. Jaussent I, Bouyer J, Ancelin ML, et al. Excessive sleepiness is predictive of cognitive decline in the elderly. Sleep. 2012; 35(9): 1201–1207.
58. Gjerstad MD, Aarsland D, Larsen JP. Development of daytime somnolence over time in Parkinson's disease. Neurology. 2002; 58(10): 1544–1546.
59. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 1991; 82(4): 239–259.
60. Wang P, Wing YK, Xing J, et al. Rapid eye movement sleep behavior disorder in patients with probable Alzheimer's disease. Aging Clin Exp Res. 2016; 28(5): 951–957.
61. Poryazova R, Benninger D, Waldvogel D, Bassetti CL. Excessive daytime sleepiness in Parkinson's disease: characteristics and determinants. Eur Neurol. 2010; 63(3): 129–135.
62. Shpirer I, Miniovitz A, Klein C, et al. Excessive daytime sleepiness in patients with Parkinson's disease: a polysomnography study. Mov Disord. 2006; 21(9): 1432–1438.

SUPPLEMENTARY MATERIAL

Supplementary Material is available at *SLEEP* online.

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AUTHOR CONTRIBUTIONS

JYZ contributed to the study concept and design, statistical analysis, interpretation of the data, and drafted the manuscript. JHZ contributed to the study concept and design, interpretation of the data, and a critical revision of the manuscript for important intellectual content. SPL, JWYC, VM and AC contributed to the acquisition of the data and clinical assessment. SXL contributed to the interpretation of the data and a critical revision of the manuscript for important intellectual content. YPL contributed to the analysis and interpretation of the data. XDT and WHY contributed to the study design and interpretation of the data. YKW contributed to the study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, study supervision, and obtaining funding. All the authors reviewed the manuscript and approved the final version.

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