Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Phenoconversion from Idiopathic Rapid Eye Movement Sleep Behavior Disorder to Lewy Body Disease

Tomoyuki Miyamoto, MD, PhD[1,*] *and Masayuki Miyamoto, MD, PhD*[2]

ABSTRACT: Background: The conversion rate and estimated risk of neurodegenerative diseases vary with idiopathic rapid eye movement sleep behavior disorder (IRBD).

Methods: This retrospective cohort study examined 273 patients (213 men, 60 women) with polysomnographic-confirmed IRBD (192 and 81 patients in the Sleep Center [SC] cohort and Neurological Center [NC] cohort, respectively) who were followed longitudinally. The date of diagnosis was determined as the onset of an overt neurological syndrome. The conversion rate was calculated; the risk of developing an overt neurological syndrome was estimated using the Kaplan-Meier method.

Results: The estimated onset risk for a neurodegenerative syndrome from the time of IRBD diagnosis when the SC and NC cohorts were combined was 11.9%, 20.3%, 33.2%, and 51.4% at three, five, seven, and ten years, respectively. The phenoconversion rate (21.7% with a mean follow-up period from the time of IRBD diagnosis of 3.9 ± 3.0 years) was lower than in prior studies, but the conversion risk increased progressively as the follow-up period increased. The majority of patients developed Lewy body disease, while multiple system atrophy was rare. The risk of developing Lewy body disease differed significantly between the SC and NC cohorts (P = 0.02).

Conclusions: In this first study of a large Asian IRBD population, the estimated conversion risk leading to diagnosis differed between the two cohorts, which could be attributed to different evaluation results depending on the observed population due to a referral bias and follow-up duration. Researchers should be aware of potential selection bias in their clinical studies.

Introduction

Rapid eye movement sleep behavior disorder (RBD) is a parasomnia that is characterized by dream-enacting behaviors, unpleasant dreams, and lack of muscle atonia during rapid eye movement (REM) sleep. RBD has historically been classified as primary or idiopathic when it occurs in the absence of associated comorbidities or provoking factors, and as secondary when it is precipitated by medications (predominantly antidepressants) or is associated with other neurological or neurodegenerative disorders, autoimmune diseases, or brainstem lesions.[1] Longitudinal studies conducted in sleep centers demonstrated that patients diagnosed with idiopathic RBD (IRBD) would eventually be diagnosed with synucleinopathies (i.e., Parkinson's disease [PD], dementia with Lewy bodies [DLB], and multiple system atrophy [MSA].[2] IRBD is recognized as the prodromal stage of an α-synucleinopathy.[1] The estimated risk of subjects with IRBD developing an overt neurodegenerative syndrome such as DLB, PD, or MSA varies between different centers.[3–9] These studies, with increasing follow-up times, showed that >80% of such patients eventually converted from IRBD to an overt neurological syndrome.

The current retrospective cohort study aimed to provide an estimated risk of developing a neurodegenerative syndrome, with

[1]*Department of Neurology, Dokkyo Medical University Saitama Medical Center, Saitama, Japan;*[2]*Center of Sleep Medicine, Dokkyo Medical University Hospital, Tochigi, Japan*

***Correspondence to**: Tomoyuki Miyamoto MD. PhD, Professor and Chairman, Department of Neurology, Dokkyo Medical University Saitama Medical Center, 343-8555, Japan; miyatomo@dokkyomed.ac.jp
Keywords: dementia with Lewy bodies, Lewy body disease, Parkinson's disease, phenoconversion, REM sleep behavior disorder.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 17 January 2018; revised 29 April 2018; accepted 24 May 2018.
Published online 3 October 2018 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mdc3.12647

medium- and long-term follow-up of Japanese patients with IRBD, by investigating differences between cohorts from two facilities, a Sleep Center and a Neurological Center.

Methods

A total of 273 patients with IRBD were examined in the current study as follows: 192 patients (152 men, 40 women) who attended the Center of Sleep Medicine of Dokkyo Medical University Hospital (Sleep Center cohort) between October 2005 and September 2017; and 81 patients (61 men, 20 women) who attended the Neurological Department of Dokkyo Medical University Saitama Medical Center (Neurological Center cohort) between June 2011 and September 2017 (Fig. 1). The neurological and sleep centers are both parts of University Hospital but are located in medical zones approximately 100 km away from each other in the Kanto region of Japan. Therefore, they are located in independent medical service areas, and patients do not visit both facilities. Patients suspected of having RBD due to abnormal behavior during sleep are referred to either center by a primary care physician (home doctor). If a patient attends either facility without a referral letter, they are instructed to bring a letter of introduction from their personal physician before they are examined.

All patients had a history of recurrent behavior of acting out dreams, which was confirmed by video-polysomnography. RBD was diagnosed according to the International Classification of Sleep Disorders, second edition.[10] IRBD patients were followed systematically every 1–3 months at the sleep center and neurological center by neurologists with expertise in both sleep disorders and neurological disorders (TM, MM). At each visit, these neurologists performed a comprehensive neurological examination and took a detailed clinical history, during which the patients and their accompanying spouses and relatives were questioned systematically regarding cognition and motor problems. If during these follow-up assessments, the appearance of symptoms or signs suggestive of motor or cognitive impairment was detected, these neurologists assessed the patients through a neurological examination, including the Unified Parkinson's Disease Rating Scale III,[11] and a neuropsychological test (Mini-Mental State Examination[12] and/or Montreal Cognitive Assessment).[13] The onset of an overt neurodegenerative syndrome (PD, DLB, and MSA) was determined as the date of diagnosis according to the accepted clinical criteria,[14–16] and was recorded in the patient's medical records. More detailed definitions of the overt neurodegenerative syndromes are as follows. The occurrence of parkinsonism was defined as the presence of bradykinesia that impaired the activities of daily living in association with rigidity, resting tremor, or postural instability. DLB was defined as the presence of obvious visual hallucinations and progressive cognitive impairments with fluctuating cognition with pronounced variations in attention and alertness, which impaired the activities of daily living. Follow-up duration was defined as the interval from the diagnosis of IRBD to the time of the last visit or death. If a new diagnosis of PD[17] or DLB[18] was made during the 2017 assessments, the date of the assessment was used as the onset of the condition. The duration of any emerging overt neurodegenerative syndrome was defined as the interval between the time of its diagnosis and that of the last follow-up assessment or death. The conversion rate was calculated using the mean follow-up period from the time of IRBD diagnosis. The risk of developing an overt neurodegenerative syndrome from the time of IRBD diagnosis was estimated using the Kaplan-Meier method.

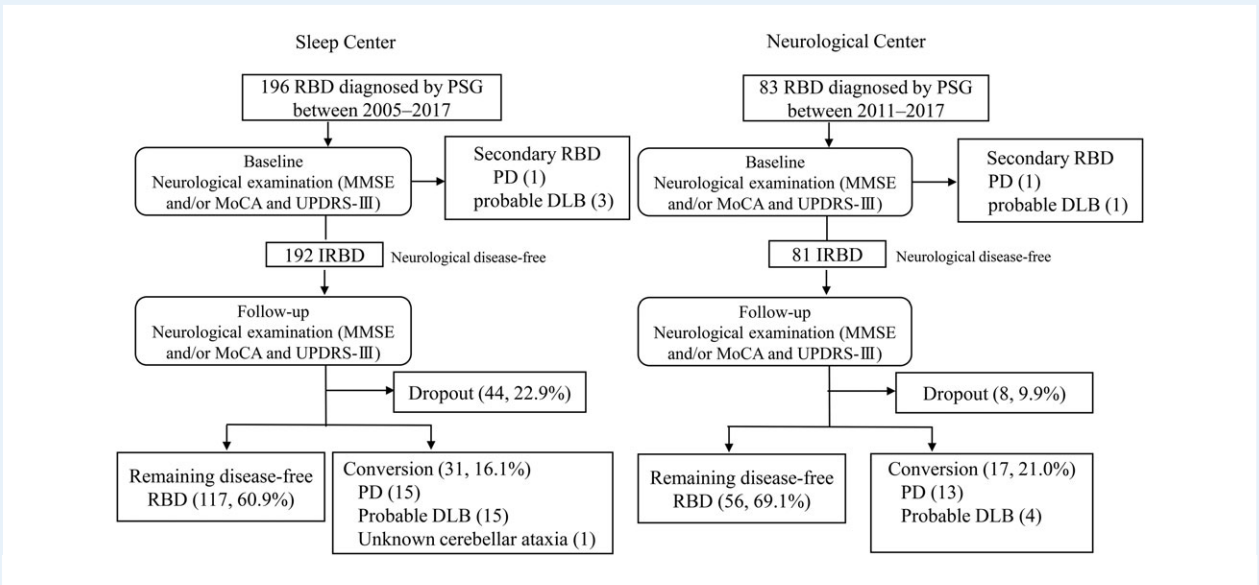

FIG. 1. Study flow chart of the follow-up of patients with idiopathic rapid eye movement disorder (IRBD). MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; PD, Parkinson's disease; pDLB, probable dementia with Lewy bodies; PSG,polysomnography; UPDRS, Unified Parkinson's Disease Rating Scale.

TABLE 1 *This study of IRBD showing conversion to a defined overt neurodegenerative disease*

	Sleep Center cohort between 2005–2017	Neurological Center cohort between 2011–2017	Combined Sleep Center and Neurological center cohort
Number of patients	192	81	273
Men /Women	152/40 (79.2%, men)	61/20 (75.3%, men)	213/60 (78.0%, men)
Mean age at RBD estimated onset, years (mean ± SD)	60.4 ± 9.2	63.0 ± 8.3	61.1 ± 9.0
Mean age at IRBD diagnosis, years (mean ± SD)	67.6 ± 6.7	68.1 ± 6.7	67.7 ± 6.6
Mean age at the time of the study outcome, years (mean ± SD)	71.5 ± 7.1	71.3 ± 6.7	71.4 ± 6.9
Mean follow-up time from IRBD estmated onset, years (mean ± SD)	11.1 ± 7.7	7.8 ± 6.1	10.2 ± 7.4
Mean follow-up time from IRBD diagnosis, years (mean ± SD)	3.8 ± 3.2	2.7 ± 2.0	3.5 ± 3.0
Mean follow-up time from IRBD diagnosis, excluded dropout cases, years (mean ± SD)	4.4 ± 3.3	2.8 ± 2.0	3.9 ± 3.0
Conversion rate (%), excluded dropout cases	20.9	23.3	21.7
Risk for conversion from IRBD diagnosis	10.3% at 3 years; 15.8% at 5 years; 26.4% at 7 years; 46.5% at 10 years	17.4% at 3 years; 31.2% at 5 years; 74.2% at 7 years	11.9% at 3 years; 20.3% at 5 years; 33.2% at 7 years; 51.4% at 10 years
Number of patinets with emergining ND	15 patients with PD; 15 patients with DLB; 1 patient with unknown cerebellar ataxia	13 patients with PD; 4 patients with DLB	28 patients with PD; 19 patients with DLB; 1 patient with unknown cerebellar ataxia
Mean time interval between RBD estimated onset and ND diagnosis, years (mean ± SD)	11.8 ± 8.1	7.2 ± 5.3	10.2 ± 7.5
Mean time interval between IRBD diagnosis and ND diagnosis, years (mean ± SD)	4.4 ± 3.3	3.0 ± 2.0	3.9 ± 3.0
Mean age at ND diagnosis, years (mean ± SD)	73.1 ± 6.6	70.0 ± 9.0	72.0 ± 7.6

IRBD = idiopathic rapid eye movement disorder. RBD = rapid eye movement disorder. ND = neurodegenerative disease. PD = Parkinson disease. DLB = dementia with Lewy bodies.

This study was performed in accordance with the Declaration of Helsinki, and the Ethics Review Committee of Dokkyo Medical University approved it. Verbal informed consent was obtained from each subject. We informed the subjects about this research project and established a procedure for them to opt out of the study if they did not wish to participate in it.

Results

The mean estimated onset age of RBD was 60.4 ± 9.2 years for the sleep center cohort and 63.0 ± 8.3 years for the neurological center cohort, and the mean age at the time of confirmed diagnosis was 67.6 ± 6.7 years and 68.1 ± 6.7 years, respectively. The mean interval from the onset of IRBD to a confirmed diagnosis was 7.2 ± 7.2 and 5.1 ± 5.5 years for the sleep center cohort and neurological center cohort, respectively. The mean age at the time of study outcome was 71.6 ± 7.1 and 71.3 ± 6.7 years, respectively. The mean interval from the onset of IRBD estimation to study outcome was 11.2 ± 7.7 years for the sleep center cohort and 7.8 ± 6.1 years for the neurological center cohort, while the average interval from the confirmation of diagnosis to study outcome was 3.8 ± 3.2 and 2.7 ± 2.0 years, respectively. The maximum time from diagnosis confirmation to study outcome was 13.2 years and seven years for the sleep center cohort and neurological center cohort, respectively. The follow-up period from the onset of RBD estimation for the Neurological Center cohort was shorter than that for the sleep center cohort (Table 1).

A total of 48 patients (21.7%) from the combined sleep center and neurological center cohort with a mean follow-up period from the time of IRBD diagnosis of 3.9 ± 3.0 years, consisting of 31 patients (20.9%) from the sleep center cohort and 17 patients (23.3%) from the neurological center cohort, developed an overt neurodegenerative syndrome, with a mean follow-up period from the time of IRBD diagnosis of 4.3 ± 3.2 years and 2.8 ± 2.0 years, respectively (excluding the dropout cases). In the sleep center cohort and neurological center cohort, a total of 15 (48.4%) and 13 (76.5%) patients developed PD, respectively, while 15 (48.4%) and four (23.5%) patients developed probable DLB, respectively, both of which were Lewy body disease (LBD). One patient in the Sleep Center cohort developed unknown cerebellar ataxia (Table 1).

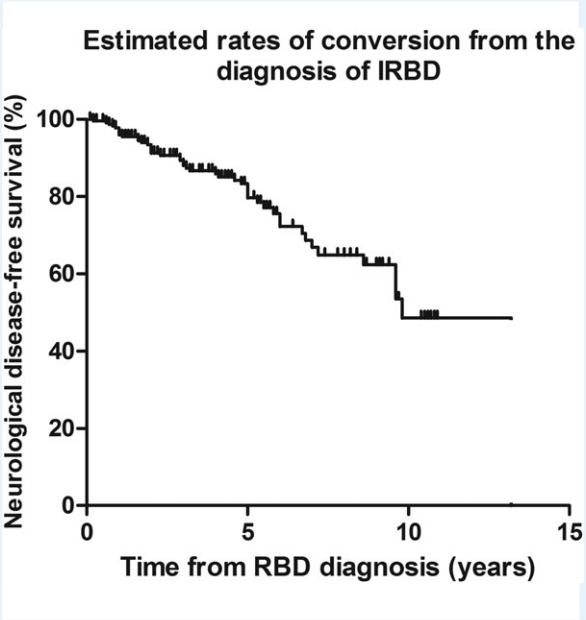

FIG. 2. Rates of neurological disease-free survival, according to the time of idiopathic rapid eye movement sleep behavior disorder (IRBD) diagnosis in the 273 patients.

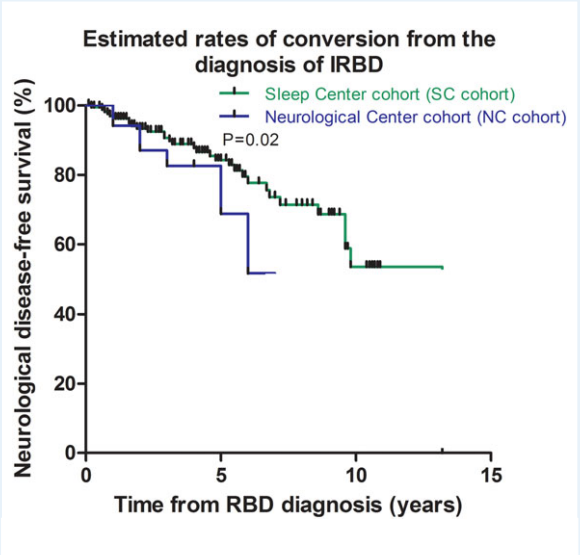

FIG. 3. Rates of neurological disease-free survival according to the time of IRBD diagnosis in the 192 and 81 patients from the sleep center and neurological center cohorts, respectively.

The estimated onset risk for an overt neurodegenerative syndrome from the time of IRBD diagnosis for the combined sleep center and neurological center cohort was 11.9%, 20.3%, 33.2%, and 51.4% at three, five, seven, and ten years, respectively (Fig. 2). The estimated onset risk for an overt neurodegenerative syndrome from the time of IRBD diagnosis for the sleep center cohort alone at three, five, seven, and ten years was 10.3%, 15.8%, 26.4%, and 46.5%, respectively, while for the Neurological Center cohort it was 17.4%, 31.2%, and 74.2% at three, five, and seven years, respectively. The risk of developing an overt neurodegenerative syndrome was significantly different between the 192 patients of the sleep center cohort and the 81 patients of the neurological center cohort ($P = 0.02$; Fig. 3).

Discussion

In this first study of a large population of Asian IRBD subjects, the estimated conversion risk leading to diagnosis differed between the two IRBD cohorts. The results of the current study corroborated those of a study conducted by a Canadian sleep disorders laboratory, in which 26 of 93 (28%) patients with IRBD developed a neurodegenerative disease after a mean follow-up period of five years. The following neurodegenerative diseases were observed: PD in 14 patients, DLB in seven patients, dementia that met the clinical criteria for Alzheimer's disease in four patients, and MSA in one patient.[6] Other cross-sectional studies demonstrated comorbid mild cognitive impairment (MCI),[6,17,19] where patients with IRBD demonstrated a similar cognitive dysfunction to that observed in LBD with regard to visuospatial ability.[6] IRBD is a known risk factor for developing MCI.[20] A substantial number of patients with IRBD progressively develop overt synucleinopathy features over time, and those who develop MCI and subsequent dementia have clinical features that are most consistent with DLB.[21] In the current study, there was no significant difference in the progression rate of neurocognitive outcome between patients with dementia with and without IRBD.[22] However, unlike a previous Spanish study,[5] MCI was not considered a disease outcome in the current study, in keeping with the Canadian study.[6] Some of this variation or limitation may be due to differences in disease definition, and we used strict criteria that may exclude patients with RBD-MCI and mild parkinsonian signs, which could have influenced the conversion rate.

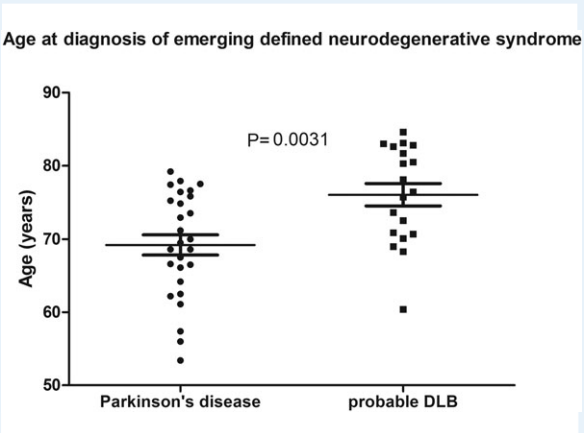

FIG. 4. Comparison of the age at diagnosis between 28 patients with Parkinson's disease and 19 patients with dementia with Lewy bodies (DLB). The *P*-value was determined using the Mann-Whitney *U*-test.

A total of 44 patients (22.9%) in the Sleep Center cohort were lost to follow-up, and two patients were excluded due to the onset of stroke. Therefore, a total of 148 patients (77.1%) completed the study, with a high dropout rate. Although the patients who were lost to follow-up were disease-free at the time of dropout, it is unknown whether or not they later developed an overt neurodegenerative syndrome. Patients who developed an overt neurodegenerative syndrome after dropout could affect the conversion rate and increase the estimated risk of developing an overt neurodegenerative syndrome. The conversion rate of the 148 patients (excluding the dropout cases) with IRBD in the sleep center cohort was lower than that of previous studies.[5,6] The Spanish sleep center IRBD cohort, who were closely followed for a median period of four years, showed survival curves indicating an estimated risk of a defined neurodegenerative disease from the time of IRBD diagnosis of 33.1%, 75.7%, and 90.9% at five, ten, and 14 years, respectively.[9] A total of 65 (37.4%) patients were clinically diagnosed with PD (n = 22), DLB (n = 29), MSA (n = 2), and MCI (n = 12). The conversion rate of our combined Japanese RBD cohort was similar to that reported from South Korea.[8] Differences between the studies, however, could be attributed to racial differences between Asians and Caucasians. However, given the similar lifestyles and living environments of the two RBD cohorts in the current study, other factors must be taken into consideration when comparing the cohorts to clarify significant differences in the conversion rate. Overall, for a short-term follow-up period, the risk of developing an overt neurodegenerative syndrome was less than the risk reported in previous American, Canadian, and Spanish studies. However, as the duration of the follow-up period increased, the risk of developing a neurodegenerative disease progressively increased.[2] For PD, the mean age at the time of study outcome was 71.2 years; however, the mean age at the time of study outcome for patients with DLB was 73.5 years (Fig. 4). In a previous prospective study, compared to PD without dementia, PD patients who developed dementia were older at baseline, Kaplan-Meier analysis estimated a 15%, 29%, and 45% risk of dementia at 2, 3, and 4 years, respectively, for PD patients with RBD, compared to 0% for PD without RBD.[23] These results suggest that the conversion rate or onset age of PD with dementia or DLB was related to age.

The difference in conversion rate for our two cohorts may be explained as follows. First, there were a large number of dropout patients in the sleep center cohort. Although phone surveys and sending out questionnaires can reduce the dropout rate, we only used data that the researchers obtained from a direct visit to improve diagnostic accuracy. Second, the study setting may have influenced the characteristics of the study population. The centers are adjacent but located in different medical zones, and the lifestyles and environments of both cohorts are similar. Clinics specializing in neurology, movement disorders, dementia, and depression and clinics specializing in sleep disorders conduct different medical examinations to assess patients. For example, in a Chinese (Hong Kong) study,[7] a comparison of the survival curves for the development of PD in IRBD patients, with and without psychiatric diagnosis, suggest that the presence of premorbid psychiatric disorders was significantly associated with an increased risk of developing PD for the overall cohort after adjusting for gender, age at RBD diagnosis, and smoking status. Psychiatric disorders, particularly depression, are a significant risk factor in predicting PD in IRBD patients, which may lend further support to a role for psychiatric disorders in predicting the emergence of PD-related pathologies. Further, in comparison to the neurological center cohort, in a recent Chinese (Shanghai) neurological center cohort study,[24] 18 of 43 patients (41.9%) developed a defined neurodegenerative synucleinopathy diseases (DLB = 2, MSA = 3, PD = 13) after a median prospective follow-up period of 4.1 years (median interval of 10.5 years from the estimated onset of IRBD symptoms). This indicates a relatively high conversion rate in previous sleep center studies.[3–9] Thus, it is necessary to consider bias in the characteristics of the patient population at each clinic. This suggests that differences in the types of neurodegenerative disease observed may occur, depending on the center visited by patients with IRBD, and the type and rate of conversion.

A strength of the current study was its high diagnostic accuracy among homogeneous populations since a neurologist qualified through the Japanese Society of Neurology and a sleep specialist qualified through the Japanese Sleep Society of Sleep Research always examined the patients directly, and each case was verified by two researchers (TM, MM). To minimize differences between the examiners' evaluations, all cases were evaluated by the same researchers (TM, MM), from the initial examination until the study outcome date. Strict criteria for consensus were used for the diagnostic criteria for overt neurodegenerative diseases.[14,15,17,18]

A few limitations of the current study include the following: (1) a shorter follow-up period than used in prior cohorts, (2) a lack of inclusion of MCI as a criterion for the onset of a neurodegenerative disease, and (3) a large number of dropout cases in the sleep center cohort.

Conclusions

In the current study, the medium- and long-term risk of developing a neurodegenerative disease was investigated in two Japanese RBD cohorts. The conversion rate was lower than that of previous American, Canadian, and Spanish studies. However, the conversion rate progressively increased as the follow-up period increased. This is the first study in a large sample of Asian IRBD subjects that confirmed the progressive increase in the risk of phenoconversion to a neurodegenerative syndrome in patients with IRBD over time. Of the neurodegenerative disease that occurred later, the majority of cases were LBD, while MSA was rare.

The difference in the estimated conversion rate between the two IRBD cohorts could be attributed to a referral bias leading to the diagnosis of IRBD, which may result in different evaluation results depending on the observed population. Researchers should be aware of potential selection bias in their clinical studies, measure it (where possible), and discuss its implications for the interpretation of a study's findings. These data give information on the development of an optimal clinical trial period for potential disease-modifying therapies.

Acknowledgments

The authors thank Drs. Keisuke Suzuki and Koichi Hirata, Department of Neurology, Dokkyo Medical University, for their help.

Author Roles

1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

T.M.: 1A, 1B, 1C, 2A, 2B, 2C, 3B

M.M.: 1A, 1B, 1C, 2A, 3A

Ethical Compliance Statement: This study was performed in accordance with the Declaration of Helsinki, and the Ethics Review Committee of Dokkyo Medical University approved it. Verbal informed consent was obtained from each subject. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Disclosures

Funding Sources and Conflicts of Interest: There are no funders to report for this submission. The authors declare that they have no potential conflicts of interest in relation to this article.

Financial disclosures for previous 12 months: The authors have no disclosures to report.

References

1. Högl B, Stefani A, Videnovic A. Idiopathic REM sleep behavior disorder and neurodegeneration – an update. *Nat Rev Neurol*. 2018;14:40–55.
2. Iranzo A, Santamaria J, Tolosa E. Idiopathic rapid eye movement sleep behaviour disorder: diagnosis, management, and the need for neuroprotective interventions. *Lancet Neurol*. 2016;15:405–419.
3. Schenck CH, Bundlie SR, Mahowald MW. Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder. *Neurology*. 1996; 46: 388–393.
4. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older males initially diagnosed with idiopathic REM sleep behavior disorder (IBD): 16 year update on a previously reported series. *Sleep Med*. 2013; 14: 744–748.
5. Iranzo A, Molinuevo JL, Santamaria J, Serradell M, Martı' MJ, et al. Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disease: a descriptive study. *Lancet Neurol*. 2006;5:572–577.
6. Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicotte-Marquez J, et al. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. *Neurology*. 2009;72: 1296–1300.
7. Wing YK, Li SX, Mok V, Lam SP, 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;83:470–472.
8. Youn S, Kim T, Yoon IY, et al. Progression of cognitive impairments in idiopathic REM sleep behavior disorder. *J Neurol Neurosurg Psychiatry*. 2016;87:890–896.
9. Iranzo A, Fernandez-Arcos A, Tolosa E, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. *PLoS One* 2014;9:e89741.
10. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*, 2ed edn. Diagnostic cording manual: American Academy of Sleep Medicine, 2007.
11. Fahn S, Elton R.L. Members of the UPDRS Development Committee. Unified Parkinson's Disease Rate Scale. In: Fahn S, Marsden CD, Calne DB, Golgstein M, eds. *Recent Developments in Parkinson's disease*. Vol 2. Florham Park, NJ: Macmillan Health Care Information; 1987: 153–163.
12. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state" A practical method for graiding the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189–198.
13. Nasreddine ZS, Philips NA, Bedirian V et al. The Monteal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53:695–699.
14. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinic-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry*. 1992;55:181–184.
15. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, et al. Diagnosis and management of dementia with Lewy bodies. Third report of the DLB consortium. *Neurology*. 2005;65:1863–1872.
16. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the United Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Diord*. 2008;23:2129–2170.
17. Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology*. 2008;71:670–676.
18. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies. Fourth consensus report of the DLB Consortium. *Neurology*. 2017;89:1–13.
19. Gagnon JF, Vendette M, Postuma RB, et al. Mild cognitive impairment in rapid eye movement sleep behavior disorder and Parkinson's disease. *Ann Neurol*. 2009;66:39–47.
20. Fantini ML, Farini E, Ortelli P, et al. Longitudinal study of cognitive function in idiopathic REM sleep behavior disorder. *Sleep*. 2011;34: 619–625.
21. Jung Y, Boot BP, Mielke MM, Ferman TJ, Geda YE, McDadade E, et al. Phenoconversion from probable rapid eye movement sleep behavior disorder to mild cognitive impairment to dementia in a population-based sample. *Alzheimer & Dementia*. 2017;8:127–130.
22. Chwiszczuk L, Breitve MH, Brønnick K, et al. REM sleep behavior disorder is not associated with a more rapid cognitive decline in mild dementia. *Front Neurol*. 2017;8:375. doi: 10.3389/fneur.2017.00375.
23. Postuma RB, Bertrand JA, Montplaisir J, et al. Rapid eye movement sleep behavior disorder and risk of dementia in Parkinson's disease: a prospective study. *Mov Disord*. 2012;27:720–726.
24. Li Y, Kang W, Yang Q, et al. Predictive markers for early conversion of iRBD to neurodegenerative synucleinopathy diseases. *Neurology*. 2017; 88:1493–1500.