Increased Risk of Dementia Among Sleep-Related Movement Disorders

A Population-Based Longitudinal Study in Taiwan

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Abstract: Sleep-related movement disorders (SRMD) are sleep disorders. As poor sleep quality is associated with cognitive impairment, we hypothesized that SRMD patients were exposed to a great risk for developing dementia. The present study was aimed to retrospectively examine the association of SRMD and dementia risk. A retrospective longitudinal study was conducted using the data obtained from the Longitudinal Health Insurance Database (LHID) in Taiwan. The study cohort enrolled 604 patients with SRMD who were initially diagnosed and 2416 patients who were randomly selected and age/gender matched with the study group. SRMD, dementia, and other confounding factors were defined according to International Classification of Diseases Clinical Modification Codes. Cox proportional-hazards regressions were employed to examine adjusted hazard ratios (HR) after adjusting with confounding factors. Our data revealed that patients with SRMD had a 3.952 times (95% CI = 1.124–4.767) higher risk to develop all-cause dementia compared with individuals without SRMD. The results showed that SRMD patients aged 45 to 64 exhibited highest risk of developing all-cause dementia (HR: 5.320, 95% CI = 1.770–5.991), followed by patients age ≥65 (HR: 4.123, 95% CI = 2.066–6.972) and <45 (HR: 3.170, 95% CI = 1.050–4.128), respectively. Females with SRMD were at greater risk to develop all-cause dementia (HR: 4.372, 95% CI = 1.175–5.624). The impact of SRMD on dementia risk was progressively increased by various follow-up time intervals (<1 year, 1–2 years, and ≥2 years). The results suggest that SRMD is linked to an increased risk for dementia with gender-dependent and time-dependent characteristics.

INTRODUCTION

Sleep is a sophisticated process involving a complex interaction of various neurotransmitter systems and an oscillation of homeostatic and circadian systems to initiate and maintain the activity. Insufficient sleep increases a risk for developing various chronic disease and conditions including obesity, diabetes, and cardiovascular diseases. Sleep disturbance is a common symptom in patients with neurodegenerative disorders with diverse etiology such as Parkinson disease. Recent studies have demonstrated that disordered sleep is associated with cognitive impairment and memory loss. Moreover, poor sleep quality has been associated with brain atrophy. As the nature of sleep disturbance is diverse, the neurocognitive consequences of sleep disturbance after onset over time remain to be determined.

Sleep-related movement disorders (SRMD) are considered as a class of sleep disorders, which is characterized by simple, stereotyped repetitive movements during sleep. Patients with SRMD are reported to experience fragmented sleep, disturbance of sleep initiation, and excessive daytime sleepiness, resulting in decreased quality of life. Among SRMD, periodic limb movement disorder (PLMD) and restless legs syndrome (RLS) are most common sleep complaints, which involve nocturnal involuntary limb movements. The prevalence of PLMD and RLS has been reported to be 3 to 10% of general population, increasing with age. Both conditions have been reported to be associated with several physical disorders and mental abnormalities. They have been linked to poor quality of life through fatigue, compromised work performance, and impaired social and family life. It has been suggested that SRMD is a common complication and comorbidity of neurodegenerative disorders such as Parkinson disease. However, the relation of SRMD such as PLMD and RLS with cognitive impairments like dementia remains sketchy.

Researches investigating relationship between sleep disorders and cognitive illness have predominantly focused on...
sleep behavior disorders and degenerative dementia. The present study was aimed to ascertain whether patients with SRMD had an elevated risk of developing all-cause dementia during more than 5 years of follow-up, using data from the National Health Insurance Research Database.

METHODS

Database

This retrospective study was conducted with an aim to investigate the association of SRMD and dementia risk using the data retrieved from the National Health Insurance Research Database (LHID) released by the Taiwan National Health Research Institute. LHID contains all original claims data of 1 million beneficiaries, randomly sampled from the registry for Beneficiaries of National Health Insurance Research Database with more than 23 million individuals enrolled into the National Health Insurance (NHI) program, the universal payer for healthcare in Taiwan. The LHID contains records on inpatient, outpatient, and ambulatory care services, covering the period from 1997 to 2010. The diagnostic coding system for disease accepted by the NHI is the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). NHI has a rigorous monitoring system to ensure that the claims for reimbursement for healthcare are based on valid diagnoses. NHI randomly audits the healthcare records to validate medical claims for diagnosis and treatment. Previous reports have shown the reliability of the diagnosis coding in the LHID. This study protocol was approved by Institutional Review Board of Tri-Service General Hospital (TSGHIRB No.: 2-104-05-045). Because data in the LHID are deidentified, the signed informed consent of participants was waived.

Study Samples

The study group and a control cohort were selected from the LHID. The diagnoses of SRMD and dementia were the basis for claims for reimbursement for relevant services rendered by the hospitals and physicians. NHI maintains stringent regulations and makes periodic auditing of claims field for reimbursement. The study group comprised all patients who had been diagnosed for SRMD based on ICD-9-CM codes 327.5 or 333.9 for the first time from 2000 to 2005 (N = 604). Patients diagnosed of SRMD before 2000 were excluded to increase the likelihood of identifying new cases. From the beginning of 2000 to the end of 2005 during which a patient was first diagnosed with SRMD, was set as the index date. We randomly selected 2416 subjects (a sample size 4-fold that of the SRMD group), frequency matched with the study cohort in terms of age, gender, and comorbidities (hypertension, diabetes, ischaemic heart diseases, hyperlipidemia, smoking, alcoholism, obesity, atrial fibrillation, Parkinson disease, cerebrovascular accident, major depression, and chronic kidney disease) were examined by Chi-square/Fisher exact test. Cox proportional hazard regression analysis was performed to calculate adjusted hazard ratios (HR), with 95% confidence intervals (CIs), for the impact of SRMD on developing dementia. To investigate the interaction of covariates in relation to the association of SRMD and dementia, we also calculated adjusted HR stratified by age (<45, 45–64, ≥65 years), gender, and follow-up time. All statistical analyses were performed with SPSS software version 22.0. A 2-tailed P value less than 0.05 was considered statistically significant.

RESULTS

A total of 604 patients diagnosed with SRMD and 2416 gender- and age-matched controls for comparison were included in this cohort study. Demographic characteristics of both groups were presented in Table 1. There were no significant differences in distribution of age, gender, and comorbidities between the study group with SRMD and the control cohort. Our data showed that over 5-year follow-up, 12.7% of SRMD patients (n = 77) developed all-cause dementia with an overall rate of 34.44 cases per 1000 person-years, whereas 89 non-SRMD individuals (3.7%) had dementia. The results revealed that patients with SRMD had a 3.952 times (95% CI = 1.124–4.767) higher risk to develop all-cause dementia compared with individuals without SRMD (Table 2). To explore whether SRMD is an age-dependent risk factor for all-cause dementia, patients were divided into 3 groups according to age, namely <45, 45 to 64, and ≥65 years. The results showed that in comparison with age/gender matched controls, SRMD patients aged 45 to 64 exhibited highest risk of developing all-cause dementia (HR: 5.320, 95% CI = 1.770–15.991), followed by patients age ≥65 (HR: 4.123, 95% CI = 2.066–6.972), and <45 (HR: 3.170, 95% CI = 1.050–4.128), respectively. We also examined if SRMD is a sex-dependent risk factor for developing dementia. The Cox regression analysis revealed that female SRMD patients had greater risk to develop all-cause dementia (HR: 4.372, 95% CI = 1.175–5.624). We next analyzed the incidence of dementia and dementia subtypes using multivariate Cox proportional hazards regression analysis based on time intervals. Our data showed that patients with SRMD were likely to develop dementia within a year after diagnosis with time-dependent characteristic (Table 3). Kaplan–Meier
Sleep-related movement disorders (SRMD) have been shown to be a cause of chronic daytime sleepiness and sleep loss. They have been suggested to have impact on cognitive function associated with sleep deprivation.13,26–28 Our finding that SRMD as a risk factor for developing dementia is postulated to be attributed to the chronic poor quality of sleep. AD has been considered as the most common cause of dementia. In contrast, our results showed that SRMD patients exhibit a higher risk of vascular dementia compared to AD. It is in an agreement with previous study that sleep disturbance and daytime sleepiness are considered as predictor for vascular dementia.29 Sleep quality has been linked to an increased risk of cardiovascular diseases.29–31 RLS and PLMD have been associated with increased risk for cardiovascular disease in the general population.15,32,33 Age is generally acknowledged as the most important risk factor for dementia. We showed that patients with SRMD are likely to develop dementia before 65. This is agreed with the results of a French population-based survey that the prevalence of RLS was 11.3% for participants between 50 and 64 years of age. It is generally accepted that women have slightly greater probability to develop dementia than men.35 The gender difference in the prevalence of dementia among SRMD patients was found in this population-based longitudinal study.

Dementia is caused when nerve cells in the brain are damaged by diseases. Several types of dementia have been attributed to brain atrophy such as AD, frontotemporal dementia, and Lewy body dementia, as well as vascular dementia. Sleep problem is considered to be a cause of neurologic disorder. Imaging studies have revealed that poor sleep quality is associated with an increased brain atrophy.10,36 Short sleep duration has been reported to contribute to age-related changes in brain structure and cognitive performance. Deposition of amyloid, a protein normally found in brain, is known to play a role in the pathogenesis of AD. Serum concentration of amyloid rises during wakefulness and drops during sleep. Recent studies have reported that nondemented individuals reporting sleep problems exhibited greater amyloid burden.24,37,38 It is suggested that sleep disorders have effects on brain health, leading to an increased risk to dementia. In addition to sleep-associated brain damage, RLS is a neurologic disorder leading to inability to sleep during the night, whereas PLMD is motor disorder diagnosed by polysomnography. It has reported to lead to insomnia, sleepiness, and problems with concentration, cognition, motivation, anxiety, and depression. RLS has been reported to be attributed to brain dopaminergic system dysfunction, leading to a motor abnormality.39 Dopaminergic deficit has been related to cognitive impairment in movement disorder patients such as Parkinson disease. It is implied that cognitive decline may develop with concomitant dopamine deficiency and lead to dementia in a long-term setting. Nevertheless, the correlation of RLS-related dopaminergic dysregulation with dementia requires further studies to elucidate.

In this study, we found no statistically significant association between the risk of dementia and those commonly accepted risk factors such as diabetes and hypertension in SRMD population. It might be explained by the nature of dementia which is acknowledged as a multifactorial disease and contribution of a single risk factor can be relatively slight and insignificant. There are several limitations to the present study. First, in this cohort study, there was an inability to validate diagnoses and objective measure of SRMD. In addition, coding error might occur in the database. We focused on the cases with clear ICD-9 definition. Second, as a retrospective longitudinal study, we had no access to the data of medication that might

### DISCUSSION

In this longitudinal study using nationwide database, we demonstrated that SRMD were associated with an increased risk to develop all-cause dementia in initially cognitively healthy individuals without comorbid neurodegenerative disorders. We found that female SRMD patients with normal cognition are more likely to develop dementia. The results indicate that increasing age was not a risk factor for developing dementia in SRMD patients. Furthermore, the impact of SRMD on dementia risk was progressively increased by various follow-up time intervals with time-dependent characteristic.

Sleep disturbance is considered as a common manifestation in demented patients. Increasing evidence has highlighted the link between sleep problem and incidence of dementia. Poor sleep quality has been shown to be a risk factor for dementia in old patients.18,19 It has been reported that daytime sleepiness is associated with cognitive impairment.20,21 Sleep fragmentation has been linked to an increased risk of AD in elderly population.22 Recent researches have demonstrated the association of sleep disturbance with incident dementia and mortality.23–25 In this longitudinal study, we found that patients with SRMD are at high risk for dementia. RLS and PLMD, 2 common types

### TABLE 1. Baseline Demographic Status and Comorbidities Compared Between SRMD Group and Comparison Cohort

| Variable          | SRMD Cohort N = 604, % | Comparison Cohort N = 2416, % | P-Value |
|-------------------|-------------------------|-------------------------------|---------|
| Age, years (SD)†  | 57.11 (16.51)           | 56.64 (15.87)                | 0.779   |
| <45               | 216 (35.76)             | 864 (35.76)                  |         |
| 45–64             | 277 (45.86)             | 1108 (45.86)                 |         |
| ≥65               | 111 (18.38)             | 444 (18.38)                  |         |
| Sex               |                         |                               | 0.999   |
| Female            | 264 (43.71)             | 1056 (43.71)                 |         |
| Male              | 340 (56.29)             | 1360 (56.29)                 |         |
| Comorbidities     |                         |                               |         |
| Hypertension      | 6 (0.99)                | 17 (0.70)                    | 0.624   |
| DM                | 18 (2.98)               | 49 (2.03)                    | 0.745   |
| IHD               | 2 (0.33)                | 8 (0.33)                     | 0.876   |
| Hyperlipidemia    | 1 (0.17)                | 1 (0.04)                     | 0.064   |
| TUD               | 0 (0)                   | 0 (0)                        |         |
| Alcoholism        | 0 (0)                   | 0 (0)                        |         |
| Obesity           | 1 (0.17)                | 1 (0.04)                     | 0.064   |
| AF                | 0 (0)                   | 1 (0.04)                     | 0.108   |
| PD                | 1 (0.17)                | 6 (0.25)                     | 0.334   |
| CVA               | 12 (1.99)               | 40 (1.66)                    | 0.117   |
| Depression        | 4 (0.66)                | 12 (0.50)                    | 0.456   |
| CKD               | 0 (0)                   | 0 (0)                        |         |

AF = atrial fibrillation, CKD = chronic kidney disease, CVA = cerebral vascular accident, DM = diabetes mellitus, IHD = ischemic heart disease, PD = Parkinson disease, SRMD = sleep-related movement disorders, TUD = tobacco use disorder.

† t-test.
TABLE 2. Incidence of Dementia and Dementia Subtypes and Multivariate Cox Proportional Hazards Regression Analysis Measured Hazard Ratio for Study Cohort

| Variable                      | SRMD Cohort | Comparison Cohort | Crude HR (95% CI) | Adjusted HR (95% CI) |
|-------------------------------|-------------|-------------------|-------------------|----------------------|
|                               | Event       | P Ys              | Rate              |                      |
| All-cause dementia            | 77          | 2236              | 34.44             |                      |
| AD                            | 5           | 2236              | 2.24              |                      |
| VD                            | 18          | 2236              | 8.05              |                      |
| <45 years                     |             |                   |                   |                      |
| All-cause dementia            | 41          | 930               | 44.09             |                      |
| AD                            | 2           | 930               | 2.15              |                      |
| VD                            | 9           | 930               | 9.68              |                      |
| 45–64 years                   |             |                   |                   |                      |
| All-cause dementia            | 26          | 1025              | 25.37             |                      |
| AD                            | 1           | 1025              | 1.95              |                      |
| VD                            | 5           | 1025              | 4.88              |                      |
| ≥65 years                     |             |                   |                   |                      |
| All-cause dementia            | 10          | 281               | 35.59             |                      |
| AD                            | 1           | 281               | 3.56              |                      |
| VD                            | 4           | 281               | 14.23             |                      |
| Male                          |             |                   |                   |                      |
| All-cause dementia            | 32          | 1261              | 25.38             |                      |
| AD                            | 2           | 1261              | 1.59              |                      |
| VD                            | 9           | 1261              | 7.14              |                      |
| Female                        |             |                   |                   |                      |
| All-cause dementia            | 45          | 975               | 46.15             |                      |
| AD                            | 3           | 975               | 3.08              |                      |
| VD                            | 9           | 975               | 9.23              |                      |

Model adjusted for age, sex, hypertension, DM, IHD, hyperlipidemia, TUD, alcoholism, obesity, AF, PD, CVA, depression, and CKD. AD = Alzheimer disease, AF = atrial fibrillation, CKD = chronic kidney disease, CVA = cerebral vascular accident, DM = diabetes mellitus, IHD = ischemic heart disease, PD = Parkinson disease, PYs = person-years, Rate = incidence rate, per 1000 person-years, SRMD = sleep-related movement disorders, TUD = tobacco use disorder, VD = vascular dementia.

* P < 0.05.
** P < 0.01.
*** P < 0.001.

TABLE 3. Incidence of Dementia and Dementia Subtypes and Multivariate Cox Proportional Hazards Regression Analysis Measured Hazard Ratio for Study Cohort by Various Time Intervals

| Variable                      | SRMD Cohort | Comparison Cohort | Crude HR (95% CI) | Adjusted HR (95% CI) |
|-------------------------------|-------------|-------------------|-------------------|----------------------|
|                               | Event       | P Ys              | Rate              |                      |
| Follow <1 year                |             |                   |                   |                      |
| All-cause dementia            | 36          | 123               | 292.68            |                      |
| AD                            | 3           | 123               | 24.39             |                      |
| VD                            | 8           | 123               | 65.04             |                      |
| Follow ≥1, <2 years           |             |                   |                   |                      |
| All-cause dementia            | 20          | 175               | 114.29            |                      |
| AD                            | 1           | 175               | 5.71              |                      |
| VD                            | 6           | 175               | 34.29             |                      |
| Follow ≥2 years               |             |                   |                   |                      |
| All-cause dementia            | 21          | 1938              | 10.84             |                      |
| AD                            | 1           | 1938              | 0.52              |                      |
| VD                            | 4           | 1938              | 2.06              |                      |

Model adjusted for age, sex, hypertension, DM, IHD, hyperlipidemia, TUD, alcoholism, obesity, AF, PD, CVA, depression, and CKD. AD = Alzheimer disease, AF = atrial fibrillation, CKD = chronic kidney disease, CVA = cerebral vascular accident, DM = diabetes mellitus, IHD = ischemic heart disease, PD = Parkinson disease, PYs = person-years, Rate = incidence rate, per 1000 person-years, SRMD = sleep-related movement disorders, TUD = tobacco use disorder, VD = vascular dementia.

* P < 0.05.
** P < 0.01.
*** P < 0.001.
have effects on SRMD and/or dementia. Third, as baseline risk factor was used, changes in risk factor profile during follow-up may need to be considered for the effect on association. In addition, we were unable to distinguish the causal relationship between SRMD and dementia based on the study population. Although the data collection was extensive, lack of information on some adaptable risk factors, such as physical activity, dietary habits, depression, education, and social engagement might lead to a misinterpretation of the results.

In conclusion, we provided subjective evidence supporting the hypothesis that patients with SRMD are at relatively high risk of developing dementia. SRMD is suggested to be a gender-dependent and time-dependent risk factor of dementia. Further studies are required to elucidate the mechanism underlying the association revealed in this study.

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