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RETRACTION: SLEEP-DISORDERED BREATHING IN PATIENTS WITH PARKINSON'S DISEASE

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Following investigations of duplicate publication in Parkinsonism and Related Disorders 2009; 15: 670–674, we have determined that there is indeed a substantial overlap between the two articles. As such, we fully retract this paper from the published record of the Singapore Medical Journal.

Professor Teo Eng Kiong
Editor, Singapore Medical Journal

Sleep-disordered breathing in patients with Parkinson's disease

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ABSTRACT

Introduction: There are limited studies reporting the frequency of sleep-disordered breathing (SDB) in Parkinson's disease (PD), and the figures quoted are variable, ranging from 2.5 to 66 percent. This study aimed to determine the prevalence and types of SBD in PD patients attending the Universiti Kebangsaan Malaysia Medical Centre neurology clinic, and the correlation between the subjective sleep symptoms using the Parkinson's disease sleep scale (PDSS) and the objective measurements using polysomnography (PSG).

Methods: This was a cross-sectional study involving 46 PD patients over a period of six months. The patients' demographic data, Hoehn and Yahr staging and PDSS scores were collected. The patients were then subjected to overnight PSG using the Somnomedic system.

Results: There were 27 male and 19 female patients with a mean age of 64.0 +/- 9.7 years. 29 were Chinese, 15 Malay and 2 Indian. The mean duration of illness was 5.8 +/- 4.3 years. The mean PDSS score was 120.3 +/- 13.5. SDB was found in 54.6 percent of the patients (apnoea-hypopnoea index [AHI] 5 and above), with 27.3 percent having moderate and severe SDB (AHI 15 and above). The median AHI was 6.7 (range 0–40.4). The prevalence of SDB in PD patients based on the AHI cutoffs were 27.3 percent for mild, 18.2 percent for moderate and 9.1 percent for severe. There were statistically significant positive correlations between the AHI and the neck circumference and between the AHI and the waist-hip ratio. There was no significant correlation between the AHI and PDSS, or the AHI and disease severity.

Conclusions: There was a high prevalence of SBD in our PD patients, which was comparable to other studies. Obstructive sleep apnoea was the dominant type of SBD. There was no correlation between the subjective sleep symptoms using the PDSS and the objective measurements using PSG.

Keywords: sleep-disordered breathing, Parkinson's disease, Parkinson's disease sleepiness scale, polysomnography

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INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease affecting 1% of individuals over the age of 60 years.[1] PD was first described by James Parkinson in 1817 as the "shaking palsy".[1] It is characterised by motor symptoms, such as bradykinesia, rigidity, resting tremor and postural instability, and non-motor symptoms, such as fatigue, depression, hallucination and sleep disorders, which are more difficult to treat.

Sleep disorders, which are prevalent in PD patients, vary from 60% to 98%.[2,3] It is contributed in part by the progression of the disease, normal aging, comorbid illnesses, depression and medications used for the treatment of PD. Sleep disorders are known to impair cognition and affect the quality of life of these patients, most frequently as a result of sleep fragmentation and excessive daytime sleepiness,[4] especially in the older age group. The sleep pattern tends to change both quantitatively and qualitatively. There is evidence that PD patients tend to die more frequently in the early hours of the morning from respiratory insufficiency compared to patients with other neurological disorders.[5] Upper airway resistance syndrome and other forms of sleep apnoea syndrome, including obstructive, central and mixed types, can all be present in PD patients. Maria et al found that 66% of their PD patients had significantly higher sleep-disordered breathing (SDB) than the controls, with correlations between the severity of PD and SDB.[6] Arnulf et al reported 20% SDB in their series.[7] Many earlier studies used questionnaires to correlate sleep disorders in PD patients, but the data of SDB among PD patients in Asia is still lacking.[8,9]

The aim of this study was to determine the presence and types of SDB in a cohort of PD patients in Universiti Kebangsaan Malaysia, Medical Centre (UKMMC),

Table I. Baseline demographics.

Clinical characteristic	Mean ± SD (range)/ No. (%)
Age (years)	64.0 ± 9.7
Body mass index (kg/m^2)	24.4 ± 4.2 (16.0–35.7)
Neck circumference (cm)	36.7 ± 4.3 (29.0–48.0)
Waist-hip ratio	0.9 ± 0.1 (0.8–1.1)
Duration of disease (years)	5.8 ± 4.4 (0.8–18.0)
Hoehn and Yahr disability score	2 ± 1 (1–4)
Stage 1	10 (21.7)
Stage 2	15 (32.6)
Stage 3	15 (32.6)
Stage 4	6 (13.0)
Parkinson's disease sleep scale	120 ± 14 (75–145)
Items 14 & 15 (daytime sleepiness)	16 ± 4 (2–20)
Smoking history	
Current smokers	0 (0.0)
Ex-smokers	8 (17.4)
Never smoked	38 (82.6)
Comorbid illness	
Hypertension	21 (45.7)
Diabetes	10 (21.7)
Hyperlipidaemia	4 (8.7)
Ischaemic heart disease	3 (6.5)
Medications	
Dopamine agonist	2 (4.3)
Levodopa	27 (58.7)
Dopamine agonist & levodopa	16 (34.8)
None	1 (2.2)

SD: standard deviation

Table II. Types of SDB in PD patients.

Type of SDB	No. (%) (n = 24)
Obstructive sleep apnoea	21 (87.5)
Central sleep apnoea	0 (0.0)
Mixed sleep apnea	3 (12.5)

SDB: sleep-disordered breathing; PD: Parkinson's disease

Malaysia, using polysomnography (PSG). It also aimed to determine the correlation between the subjective (using the Parkinson's disease sleep score [PDSS] questionnaire) and objective (using PSG) measures of SDB in these patients. We postulate that Asians, who tend to have smaller body mass indexes and slightly different anthropometric features, may differ from the Caucasians, especially with regard to the variety of SDB. This study was done as part of a larger study on the types of sleep disorders.

METHODS

The inclusion criteria included patients above 18 years of age with idiopathic PD (as defined in the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria) Stages 1 to 4 according to the Hoehn and Yahr classification.[10] The exclusion criteria were patients with: (1) idiopathic Stage 5 PD; (2) neuropsychiatry symptoms; (3) secondary Parkinsonism, such as drug-induced Parkinsonism, encephalitis and anoxic brain damage; and (4) Parkinson-plus syndromes, such as progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration and diffuse Lewy body disease. Patients on sedatives such as benzodiazepine, and those with a past and known history of excessive alcohol consumption were excluded. Patients who were uncooperative and who did not sign the informed consent form were also excluded.

51 patients who fulfilled the inclusion and exclusion criteria were recruited from the UKMMC neurology clinic over a period of six months. Of these, 44 successfully completed the study, five withdrew in the beginning for various reasons and two PSGs could not be analysed due to technical fault. The patients' data collected included age, race, gender, weight, height, body mass index (BMI), neck circumference (NC) at the level of the cricothyroid membrane, waist circumference measured midway between the lower rib margin and superior iliac spine, hip circumference (widest circumference over the greater trochanters), waist-hip ratio (WHR), the duration of PD, smoking history, comorbidities and medications. The severity of PD was assessed using the Hoehn and Yahr staging scale. The subjective severity of SDB was assessed using the PDSS, a visual analogue scale used to assess sleep disturbance in PD patients.[11] The PDSS consists of 15 items that assesses areas such as insomnia (items 2 & 3), nocturia (items 8 & 9), nocturnal motor symptoms (items 10–13) and daytime sleepiness (items 14 & 15 assess morning sleepiness and unexpected dozing during the day). All the data obtained, including the translation of the PDSS questionnaires for those with limited command of the English language, was handled by a single person so as to minimise bias.

The participants underwent a full overnight PSG using the Somnomedics PSG system (Somnomedic, Hoerbergh, Warbargh, Germany) from 10 pm to 6 am to assess the objective severity of the SDB. Each PSG included an electroencephalogram with channels C3/A2 and C4/A1 used to score sleep, an electromyogram on the chin and each anterior tibialis, an electrooculogram LOC-A1/A2 and ROC-A1/A2 used to record eye movements, an electrocardiogram, a nasal airflow sensor, chest and abdomen belts, a pulse oximeter, a snore microphone and body sensors. Total sleep time (TST), sleep efficiency, sleep latency, sleep stages, arousals, snore indexes and respiratory events were scored. The severity of SDB was assessed based on the apnoea-hypopnoea index (AHI) with an AHI between 5–15 per

Table III. Comparison between patients with and without SDB.

	Mean ± SD/ median (range)		p-value
	SBD present (n = 24)	SBD not present (n = 20)	
Age (years)	64.8 ± 11.3	62.8 ± 8.1	0.50
Body mass index (kg/m^2)	25.0 ± 4.0	23.8 ± 4.8	0.35
Neck circumference (cm)	38.1 ± 4.1	35.3 ± 3.8	0.03*
Waist-hip ratio	0.93 ± 0.08	0.89 ± 0.11	0.11
Duration (years)	5.8 ± 4.7	5.8 ± 4.2	0.99
PDSS	119.9 ± 16.1	121.4 ± 10.5	0.74
PDSS items 14 & 15	17.1 (1.9–19.5)	17.3 (13–20)	0.21
Snore index (per min)	58.3 ± 97.9	20.5 ± 61.8	0.04*

NB: Tests were performed using the Student's *t*-test and Mann-Whitney U-test.
SDB: sleep-disordered breathing; SD: standard deviation; PDSS: Parkinson's disease sleep scale
* p-value < 0.05 is significant.

Table IV. Comparison between mild and severe Parkinson's disease patients.

	Mean ± SD/median (range)		p-value
	Hoehn and Yahr Stage 1 & 2 (n = 24)	Hoehn and Yahr Stage 3 & 4 (n = 20)	
Total sleep time (min)	321.1 ± 59.6	358.5 ± 113.2	0.034*
Sleep latency (min)	15.3 (3–60)	33.5 (0-224)	0.005*
Sleep efficiency (%)	81.5 (49.8–96.7)	66.3 (5.9–93.1)	0.06
Apnoea-hypopnoea index (per hr)	9.6 (0–40.4)	5.1 (0.2–28.3)	0.29
PDSS	122.7 ± 14.6	118 ± 12.4	0.26

NB: Tests were performed using the Student's *t*-test and Mann-Whitney U-test.
PDSS: Parkinson's disease sleep scale; SD: standard deviation
* p-value < 0.05 is significant.

hour considered mild SDB, 15.1–30 per hour moderate and > 30 per hour severe, according to the British Thoracic Society guidelines.[12] The study was approved by the Medical and Research Ethics Committee of the Faculty of Medicine, UKMMC, Malaysia.

Statistical analysis was done using the Statistical Package for Social Sciences version 12.0 (SPSS Inc, Chicago, IL, USA). Categorical and continuous data were examined for frequencies, characteristics and distribution. Continuous data was further explored to check the normality and equality of variance assumptions. Normally distributed parametric data was expressed as mean ± standard deviation, and non-parametric data was expressed as median (range). Parametric data was analysed using an independent samples *t*-test, while non-parametric data was analysed using the Mann-Whitney U test. Correlations between two continuous variables were examined using the Spearman's rank order correlation test. Any p-value ≤ 0.05 was deemed significant.

RESULTS

The demographic and clinical characteristics of the patients are summarised in Table I. SDB was observed in 24 (54.6%) local PD patients (AHI ≥ 5/hr), while 27.3% had moderate and severe SDB (AHI ≥ 15/hr). The prevalence of SDB in PD patients depending on AHI cutoffs were 27.3% for mild, 18.2% for moderate and 9.1% for severe. 27.3% had mild, 18.2% moderate and 9.1% severe SDB. The median AHI was 6.8/hr (range 0.0–40.4/hr). The three types of SDB noted are shown in Table II. There was a significant difference in the NC and snore indexes between the patients with SDB and those without SDB (Table III).

10 (21%) patients were in Stage 1, 15 (32.6%) in Stage 2, 15 (32.6%) in Stage 3 and another 6 (13%) in Stage 4 of the Hoehn and Yahr staging scale. There was no significant difference between mild PD (Stages 1 & 2) and severe PD (Stages 3 & 4) in terms of the AHI, as measured by the PSG and PDSS scores. However, there were significant differences in TST and sleep latency between the patients with mild and severe PD (Table IV).

There was a significant positive correlation between the AHI and NC ($r = 0.418$, $p = 0.005$). There was also a positive correlation between the AHI and WHR ($r = 0.341$, $p = 0.024$). There was no significant correlation between the AHI and PDSS or the AHI and disease severity based on the Hoehn and Yahr scores. We did not observe any correlation between age, duration of disease, total daily dose of levodopa and the use of dopamine agonist with SDB.

DISCUSSION

We found a high prevalence of SDB in this cross-sectional study involving 46 PD patients in UKMMC, Malaysia over a period of six months. 54.6% of our patients had an AHI > 5/hr and, the majority were mild to moderate types. Similar findings were also noted by Maria et al, who found that ten (66.1%) out of 15 patients had SDB.[6] Arnulf et al, who conducted a study on 54 PD patients with daytime sleepiness, found that 20% of these patients had moderate to severe SDB, which was similar to our results, although our patients were mostly asymptomatic based on the PDSS.[7] This prevalence is however far greater than those found in the Wisconsin sleep cohort study on elderly Americans, which found a prevalence of 24% and 9% in men and women, respectively, with an AHI > 5/hr.[13]

Although there are conflicting data in previous studies, we found obstructive sleep apnoea (OSA) (87.5%) to be the most common type of SDB among our patients.[6,7,14] One study found that 90% of the SDB patients had OSA, and only 10% had central sleep apnoea (CSA),[6] while another study found more CSA than OSA in patients with PD.[14] Since the majority of our patients were non-smokers (82.6%) and were not known to have any functional or anatomical pulmonary diseases, we hypothesised that the high prevalence of SDB in our PD patients may be due to muscular dysfunction of the upper airway, which may be related to the PD itself. (We have not substantiated our hypothesis with lung function tests on our patients as the machine was under repair at the time of this study). A study by Vincken et al in 1984 found abnormal flow-volume loop contours in 24 patients with Parkinsonism with rhythmic (4–8 Hertz) and irregular involuntary movements at the level of the glottic and supraglottic structures on direct visualisation.[15] Quanjer et al also noted abnormal flow or volume loop during spirometry in their PD patients.[16] However, Maria et al found that the forced expiratory volume in one second (FEV1), the forced vital capacity (FVC) and the FEV1/FVC were predicted to be within normal limits but noted significant differences in the maximum inspiratory and maximum expiratory pressures between PD patients and normal controls.[6] All these suggest abnormalities in the upper airway, resulting in the high prevalence of SDB in PD patients.

We noted that our PD patients with SDB did not exhibit the typical features of SDB in the normal population, such as excessive daytime sleepiness (EDS). We did not find significant correlation between SDB and BMI, a classical risk factor for SDB in the non-PD population. Our patients were mostly non-obese, with a BMI of 25.0 ± 4.0 kg/m^2, although patients with SDB had thicker NC, with positive correlations between SDB and WHR, another known risk factor. We found that PD patients with SDB had more significant snoring compared to those without, based on the PSG snoring indexes, although it was not explored as a symptom.

We assessed the use of PDSS in correlation with SDB and specifically studied the EDS component of the PDSS as an indicator of nighttime sleep disturbance in our patients. Our results showed a trend which suggested that the more advanced the PD, the worse the symptoms, as reflected by the lower PDSS scores, although this was not statistically significant. The analysis of items 14 and 15 of the PDSS questionnaire suggested a lack of daytime sleepiness in our patients with SDB (Table IV). We were unsure if the lack of sensitivity of the PDSS score in picking up SDB in our patients was somewhat related to the lack of comprehension of the questionnaire, as many of our patients had a poor command of the English language. Some patients needed translation in order to complete the questionnaires, although all the questionnaires were administered in the presence of one common doctor. Devising similar scales in the three native languages might help improve the sensitivity in our PD populations.

There was a high prevalence of SDB (54.6%) among the PD patients in our study. 87.4% of the SDB were OSA, and the rest was of a mixed type with no CSA. Although the PDSS showed a trend toward identifying the severity of PD, there was no correlation between the subjective sleep symptoms using PDSS as a whole and the objective measurements using PSG. PD patients with SDB in our study seemed to be less overweight and lacked the typical EDS, although they tended to have thicker NC and more significant snoring. One needs to have a high index of suspicion in order to recognise SDB in Parkinson's patients. Perhaps looking further for subtle worsening of cognition and quality of life not directly related to the progression of the disease, followed by overnight pulse oximetry or limited sleep study, may help to screen this group of patients. In these cases, PSG is still needed to confirm SDB. More studies on SDB in Parkinson's patients are needed.

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