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Obstructive sleep apnea, CPAP therapy and Parkinson's disease motor function: A longitudinal study

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ABSTRACT

Introduction: We aimed to assess, in patients with Parkinson's disease (PD), the association between obstructive sleep apnea (OSA), progression of motor dysfunction and the effect of OSA treatment.

Methods: Data were analysed from a prospective cohort study of idiopathic PD patients from a movement disorders clinic. Patients found to have OSA on polysomnography (apnea-hypopnea index [AHI] ≥15 events/h, OSA+) were offered treatment using continuous positive airway pressure (CPAP). CPAP+ was defined as an average ≥ 2 h/night use at each follow-up. Motor symptoms were assessed using the motor section of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (mUPDRS) and the Timed-Up-And-Go (TUG). Follow-up times were 3, 6 and 12 months. Mixed models were constructed, adjusting for age, sex, body mass index, levodopa equivalent dose and comorbidities.

Results: We studied 67 individuals (61.2% male) of mean age 64.7 years (SD = 10.1). Baseline mUPDRS was higher in OSA+ compared to OSA- (24.5 [13.6] *vs.* 16.2 [7.2], $p < 0.001$). Motor dysfunction increased at comparable rates in OSA- and OSA+CPAP-. However, in OSA+CPAP+, mUPDRS change was significantly lower compared to OSA- ($\beta = -0.01$ *vs.* 0.61, $p = 0.03$; $p = 0.12$ *vs.* OSA+CPAP- [$\beta = 0.39$]) and TUG change was lower compared to OSA+CPAP- ($\beta = -0.01$ *vs.* 0.13, $p = 0.002$; $p = 0.05$ *vs.* OSA- [$\beta = 0.02$]).

Conclusions: In this PD cohort, OSA was associated with higher baseline mUPDRS. In those with OSA, CPAP use was associated with stabilization of motor function (mUPDRS and TUG) over 12 months. These observations support further research to clarify the role of OSA in PD pathophysiology and motor dysfunction.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder, affecting over 1.7% of people over age 65 [1]. It results from loss of dopaminergic neurons, causing hallmark motor symptoms and non-motor symptoms including neurobehavioral disorders, cognitive impairment and sleep disorders [2].

Obstructive sleep apnea (OSA) is a common, treatable sleep disorder in the general population, characterized by recurrent upper airway obstruction during sleep, leading to intermittent hypoxemia and microarousals from sleep. In the general population, OSA is known to affect neurocognitive function, and to increase the risk of and morbidity associated with stroke [3,4]. OSA treatment can reduce morbidity and possibly mortality.

OSA and PD often coincide with one another, whether due to the high general prevalence of OSA, the higher incidence of OSA in PD, or OSA predisposing to PD. In large-scale population studies with long follow-up periods, OSA has been suggested to increase the incidence of PD [5]. Our group has found an association between OSA and PD non-motor symptoms [6], which improved with OSA treatment [7]. However, the interrelationship between OSA, OSA treatment and PD motor manifestations has not been studied. The objectives of this analysis of a prospective cohort were to (1) measure the association between OSA and PD motor symptom severity at baseline, and (2) assess the

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association between OSA, CPAP therapy, and motor symptom progression in PD.

2. Methods

2.1. Study subjects and design

A prospective cohort study was conducted with idiopathic PD patients from a Movement Disorder Clinic. Patients with sleep complaints were recruited between November 2011 and July 2014. Inclusion criteria were a clear diagnosis of idiopathic PD by the clinic neurologist according to the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria [8], ability to transfer with minimal assistance for in-laboratory polysomnography (PSG) and adequate proficiency in English or French. The exclusion criteria were having other major neurological disorders, unstable cardiac disease, uncontrolled hypertension, diabetes, active cancer, disorders with expected survival < 6 months, active treatment of OSA, or cognitive or psychiatric conditions that interfere with informed consent or study procedures.

At baseline, data collection included demographic data, medical and PD history, including Hoehn & Yahr (H&Y) stage [8], medication data and sleep habits. Patients underwent clinical evaluation and overnight PSG. PD motor symptom progression in PD was assessed using the part 3, motor section, of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (mUPDRS) [9], where a higher mUPDRS score indicates greater dysfunction. The Timed Up and Go (TUG) test was performed as a measure of functional mobility [10]. Testing was done in the "on" state, where medications were in effect. Patients' levodopa equivalent dose (LED) was calculated using standard formulas [11]. The presence of clinical rapid eye movement sleep behavior disorder (RBD) was identified by an in-house questionnaire (e.g. movements/vocalization in sleep, dream enactment, injury), as well as a validated questionnaire (Postuma), and the diagnosis was confirmed by clinical interview and presence of PSG features whenever possible [12]. Standard overnight PSG was done using the Harmonie System (Stellate, Montreal, Canada), with recordings from 6 EEG channels (C3, C4, F3, F4, O1 and O2); standard EMG and EOG; airflow via nasal pressure cannula; thoracoabdominal movements via inductive plethysmography (Respitrace Systems, Ardsley, NY); single-lead EKG; pulse oximetry; snoring; body position; and digital video. Non-motor symptoms were assessed using validated questionnaires, detailed in Mery 2017 [6].

OSA+ was defined as an apnea-hypopnea index (AHI) of ≥15 events/h using Chicago criteria [13]. OSA+ received counseling about OSA and were offered treatment with CPAP. Participants who agreed to CPAP therapy were treated with standard auto-PAP (initial pressure range 5–15 cm H2O, Philips-Respironics System One REMstar Auto).

Follow-up times were at 3, 6 and 12 months. Interim data collected included medical history and medication data. UPDRS, TUG and non-motor assessments were also conducted at each follow-up, in the "on" state. The type and dosage of antiparkinsonian mediation were allowed to vary over the follow-up period based on the evaluation of the treating neurologist. CPAP compliance and efficacy data were downloaded from device memory. Data included residual AHI, mean hours used per night, and % nights used > 4 h, and were used to optimize CPAP therapy.

2.2. Statistical analysis

We categorized patients at each time point based on their OSA and CPAP status: those who did not have OSA (OSA-), those diagnosed with OSA but not using CPAP (OSA+CPAP-), and those with OSA and using CPAP (OSA+CPAP+). CPAP status varied by time (3, 6 and 12 months). A patient was defined as CPAP+ for a given follow-up time period if average CPAP use was ≥2 h/night. Baseline OSA/CPAP categories (Table 1) where derived from patients' 3-month category assignments. Individuals who never used CPAP or tried CPAP but discontinued use before 3 months were categorized as CPAP-.

Baseline patient demographics and PSG data for each group were summarized using means and standard deviations (SD) or counts and proportions, where appropriate. Differences between baseline characteristics in the three OSA/CPAP categories were compared using analysis of variance (ANOVA) tests. Variables showing a significant difference in mean between overall OSA/CPAP categories were tested using Tukey's honestly significant difference (HSD) post hoc test to determine significance in difference between two groups. Differences in baseline mUPDRS and TUG between OSA categories were compared using linear regression.

Linear mixed-effects models were used to assess associations between OSA, CPAP and motor outcome progression. We included a random intercept by subject to account for the correlation between observations from the same person. Motor UPDRS score and TUG time were used as outcomes in independent models, with an interaction between OSA/CPAP group and time as the predictor. Covariates were selected a priori based on clinical associations to the primary outcome and OSA, and included age, sex and body mass index (BMI), and presence of comorbidities, defined as at least one of the following conditions found most commonly in our sample: hypertension, diabetes, any cardiac disease or hypothyroidism. Because the motor outcomes are sensitive to dopaminergic medications, we also included time varying LED at each time point.

In sensitivity analyses for the mUPDRS outcome, we assessed the effect of CPAP as a continuous variable, in average hours of use per night. In additional sensitivity analyses, we adjusted for RBD. Finally, we repeated analyses removing the highest-influencing individual. Estimates, in average change in mUPDRS per month, were presented with 95% confidence intervals (CI).

All data were analysed using R software version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/). Statistical significance levels for all tests were set to $p < 0.05$.

3. Results

3.1. Patient characteristics

A total of 243 patients with idiopathic PD were assessed for eligibility. Of these, 176 patients were excluded or not available for the study (Fig. S1). The number of participants in each OSA/CPAP category with data available for analysis at each time point are also shown in Fig. 1. Of the 67 study participants at baseline, 20 were OSA- and 47 were OSA+. Over the follow-up time, a total of 9 (13.4%) participants changed CPAP status, with most switching off CPAP therapy between 6 and 12 months.

Overall median CPAP use among patients on CPAP was 4 h 7 min/night (Min 2 h 1 min, Max 7 h 6 min/night). Median CPAP usage at 3 months among those on CPAP was 3 h 42 min/night (Min 2 h 2 min, Max 5 h 54 min/night); 4 h 7 min/night (Min 2 h 1 min, Max 7 h 6 min/night) at 6 months; and 4 h 34 min/night (Min 2 h 48 min, Max 6 h 46 min/night) at 12 months.

Baseline demographic characteristics and sleep parameters are summarized in Table 1, based on participant grouping at 3 months. PSG results showed that OSA+ had severe OSA on average with no difference in AHI between CPAP+ and CPAP-. There was increased respiratory-related sleep disruption among OSA + compared to OSA-, but this did not differ between CPAP+ and CPAP-.

In that there appeared to be differences in baseline measures of motor function across OSA- and OSA+ groups (Table 1), we compared baseline mUPDRS and TUG between OSA+ and OSA- using linear regression (Table 2). Unadjusted analysis showed a higher mUPDRS, indicating greater dysfunction, in OSA+ than in OSA-, but no significant difference in TUG scores. To account for potential confounding factors in the observed relationship between motor function and OSA, we constructed multivariable regression models with baseline mUPDRS or

Table 1
Baseline data summary.

	OSA-(n = 20)	OSA + CPAP-(n = 21)	OSA + CPAP + (n = 26)	p value[a]
Demographic Data				
Age, mean years (SD)	61.5 (8.4)	64.6 (10.8)	67.4 (10.5)	0.19
Male Sex, *n* (%)	12 (60.0)	11 (52.4)	18 (69.2)	0.50
BMI, mean kg/m^2 (SD)	26.1 (3.3)	27.5 (4.2)	29.47 (4.6)	0.02
LED, mean mg (SD)	789.8 (616.9)	848.7 (1050.4)	583.6 (416.2)	0.47
Comorbidities, *n* (%)	3 (15.0)	13 (61.9)	12 (46.2)	< 0.01
Clinical RBD, *n* (%)	7 (35.0%)	6 (28.6%)	15 (57.7)	0.10
Disease Time from Diagnosis, mean years (SD)	5.4 (3.5)	6.6 (5.9)	5.4 (6.1)	0.71
Motor UPDRS, mean (SD)	16.2 (7.2)	26.2 (14.4)	22.9 (13.7)	0.02
H&Y, mean grade (SD)	1.8 (0.7)	2.3 (0.8)	2.1 (0.9)	0.10
TUG, mean seconds (SD)	7.2 (1.8)	7.9 (2.3)	10.4 (4.9)	< 0.01
Sleep Parameters				
TST, min (SD)	322.9 (73.5)	317.5 (68.1)	328.5 (52.7)	0.85
SE, % (SD)	74.6 (15.3)	75.1 (13.5)	75.7 (12.6)	0.97
Number of Awakenings, mean (SD)	22.6 (13.9)	30.4 (15.8)	42.0 (24.9)	< 0.01
Stage changes, mean (SD)	130.6 (47.8)	172.3 (48.7)	197.9 (54.6)	< 0.01
Stage N1, % (SD)	8.1 (4.7)	13.2 (7.9)	15.9 (11.7)	0.02
Stage N2, % (SD)	53.8 (17.3)	54.4 (15.4)	55.0 (13.6)	0.97
Stage N3, % (SD)	28.2 (21.0)	22.3 (13.5)	17.8 (12.2)	0.09
REM sleep, % (SD)	9.8 (6.6)	10.1 (8.5)	11.3 (7.0)	0.78
WASO, min (SD)	96.6 (57.5)	92.0 (54.6)	96.5 (62.2)	0.96
AHI,/h (SD)	7.3 (4.2)	33.2 (13.3)	38.0 (21.5)	< 0.01
Supine AHI,/h (SD)	10.6 (5.6)	36.7 (17.3)	48.2 (30.2)	< 0.01
Non-supine AHI,/h (SD)	5.9 (3.8)	23.8 (16.4)	31.9 (24.1)	< 0.01
TST Supine, % (SD)	47.8 (23.5)	60.0 (23.5)	56.1 (30.7)	0.42
ODI,/h (SD)	0.6 (0.8)	5.4 (7.8)	12.3 (18.1)	< 0.01
Nadir SaO_2, % (SD)	88.0 (4.2)	85.7 (3.8)	83.0 (5.2)	< 0.01
Time SaO_2 < 90%, % of TST (SD)	2.8 (4.1)	4.5 (7.8)	11.8 (15.6)	0.02
Respiratory arousal index,/h (SD)	6.6 (3.9)	28.3 (12.2)	32.1 (17.5)	< 0.01
Total arousal index,/h (SD)	24.1 (8.1)	47.9 (17.5)	51.2 (18.1)	< 0.01
PLMS,/h (SD)	14.1 (25.9)	33.2 (46.7)	23.3 (34.5)	0.28
PLMA,/h (SD)	1.8 (2.7)	3.5 (4.5)	2.9 (3.6)	0.36
EES > 10, n (%)	4 (20.0)	8 (38.1)	9 (34.6)	0.46

OSA/CPAP categories are defined based on status at the 3-month follow-up. Abbreviations: AHI = Apnea-Hypopnea Index; BMI = Body Mass Index; Comorbidities = diagnosis of at least one of the following: hypertension, diabetes, any cardiac diseases or hyperthyroidism; CPAP = Continuous Positive Airway Pressure; EES = Epworth Sleepiness Scale; H&Y = Hoehn and Yahr; LED = Levodopa Equivalent Dose; ODI = Oxygen Desaturation Index; OSA = Obstructive Sleep Apnea, defined as Apnea-Hypopnea Index ≥15/h; PLMA = Periodic Limb Disorder Movements Associated with Arousal; PLMS = Periodic Limb Movements of Sleep Index; RBD = Rapid eye movement sleep behavior disorder; SE = Sleep Efficiency; TUG = Timed Up and Go; TST = Total Sleep Time; UPDRS = Unified Parkinson Disease Rating Scale; WASO = Wake After Sleep Onset .

[a] Obtained via ANOVA tests.

TUG as the outcome and diagnosis of OSA as the predictor, adjusted for patients' age, sex, BMI, LED, RBD and presence of comorbidities. We found a significantly higher mUPDRS in OSA+ compared to OSA- consistent with the unadjusted model, while the model using TUG as the outcome with the same predictor and covariates showed no difference in baseline TUG between OSA+ and OSA- individuals.

Over the follow-up period, average LED in the OSA + CPAP- group was 761.1 mg (SD = 511.6) at 3 months, 932.9 mg (1179.0) at 6 months, and 661.7 mg (446.9) at 12 months. For the OSA + CPAP + group, it was 643.1 mg (457.3) at 3 months, 524.3 mg (294.1) at 6 months and 523.2 mg (315.2) at 12 months. For the OSA- group, it was 777.2 mg (553.2) at 3 months, 722.8 mg (462.2) at 6 months and 786.4 mg (357.5) at 12 months. There were no statistically significant changes in average LED dose within any group.

3.2. Effect of OSA treatment on motor symptom progression

The average unadjusted mUPDRS and TUG scores at each timepoint are presented in Table 3. To account for potential confounding influences, we assessed the change in mUPDRS over time between groups using a linear mixed model, adjusting for age, sex, BMI, LED and comorbidities. As illustrated in Fig. 1, the model revealed mUPDRS increased over the follow-up period in OSA- (β = 0.61, 95% CI: 0.20 to 1.02) and OSA + CPAP- (β = 0.39, 95% CI: 0.00 to 0.78). The change in mUPDRS was not significantly different between OSA- and OSA + CPAP- (p = 0.45). In contrast, mUPDRS decreased in the OSA + CPAP + group (β = −0.01, 95% CI: 0.38 to 0.36, p = 0.01 *vs.* OSA-; p = 0.12 *vs.* OSA + CPAP-).

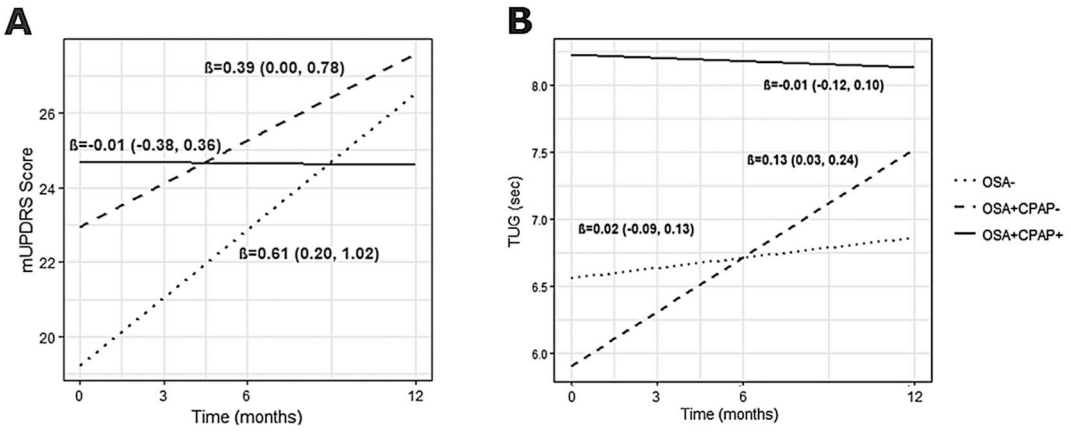
We also estimated a model with TUG as the outcome using the same predictor and covariates as for mUPDRS. The OSA + CPAP + group showed a markedly slower progression of motor symptoms compared to the OSA + CPAP- group (β = −0.01, 95% CI: 0.12 to 0.13 *vs.* β = 0.13, 95% CI: 0.03 to 0.24, p = < 0.01, Fig. 1).

We performed sensitivity analyses for the mUPDRS outcome as follows. We estimated a mixed model analysis using CPAP as a continuous variable, in average hours per night of use (Fig. S2). Progression of motor symptom severity remained comparable between OSA- and patients with OSA not using CPAP. Progression was slower with greater CPAP use, consistent with our main model, though not statistically significantly so (β = −0.05, 95% CI: 0.42 to 0.32 for average CPAP use [3 h 39 min/night]; β = −0.41, 95% CI: 0.80 to −0.02 for 95th percentile use [5 h 42 min h/night], p = 0.16).

We also included RBD as a covariate (Fig. S3). Motor UPDRS change in each group was comparable to our main model. RDB was not significantly associated with mUPDRS progression. Finally, we constructed a mixed model removing 12-month data of an outlier, which resulted in similar conclusions to the main analysis (data not shown).

4. Discussion

Our study assessed the relationship between OSA, CPAP treatment and motor symptoms in PD patients. Patients with OSA had a



	Slope[a]	p-value
mUPDRS		
OSA-	0.61 (0.20, 1.02)	ref.
OSA+CPAP-	0.39 (0.00, 0.78)	0.44
OSA+CPAP+	-0.01 (-0.38, 0.36)	0.03*, p=0.12 vs OSA+CPAP-
TUG		
OSA-	0.02 (-0.09, 0.13)	ref.
OSA+CPAP-	0.13 (0.03, 0.24)	0.46
OSA+CPAP+	-0.01 (-0.12, 0.10)	0.05, p=0.002* vs OSA+CPAP-

[a] Adjusted for sex, age, BMI, LED, RBD and comorbidities
* significance at p < 0.05

Fig. 1. Progression of Parkinson's Motor Dysfunction in Each Study Group Comparison of (A) average motor UPDRS score and (B) TUG over follow-up time in subjects with or without OSA, with or without CPAP use. Slopes (β) and their 95% CI are obtained from a mixed model, expressed as change in mUPDRS score per month. Models are adjusted for sex, age, BMI, LED and comorbidities.

Table 2
Baseline Parkinson's motor dysfunction in OSA groups.

	Unadjusted Estimate β (95% CI)	p-value	Adjusted Estimate[a] β (95% CI)	p-value
mUPDRS				
Intercept	15.85 (10.46, 21.24)	< 0.01*	15.83 (9.53, 22.14)	< 0.01*
OSA +	8.75 (2.31, 15.18)	< 0.01*	6.42 (0.02, 12.82)	0.049*
TUG				
Intercept	7.23 (5.60, 8.85)	< 0.01*	9.10 (7.49, 10.71)	< 0.01*
OSA +	1.93 (−0.02, 3.88)	0.052	1.26 (−0.43, 2.95)	0.14

* significance at p < 0.05.
[a] Adjusted for sex, age, BMI, LED, RBD and comorbidities.

Table 3
Motor dysfunction measures at each follow up time point.

		OSA-	OSA + CPAP-	OSA + CPAP +
Motor UPDRS, mean (SD)	Baseline	16.2 (7.2) N = 20	26.2 (14.4) N = 21	22.9 (13.7) N = 26
	3 months	19.1 (7.8) N = 12	23.2 (14.0) N = 13	24.4 (11.7) N = 17
	6 months	21.7 (11.8) N = 17	25.6 (18.2) N = 15	22.0 (8.5) N = 21
	12 months	22.6 (13.7) N = 15	26.4 (17.2) N = 23	26.7 (16.7) N = 18
TUG, mean seconds (SD)	Baseline	7.2 (1.8) N = 19	7.9 (2.3) N = 21	10.4 (4.9) N = 23
	3 months	7.9 (3.2) N = 12	7.5 (3.0) N = 12	8.3 (2.7) N = 16
	6 months	7.7 (2.0) N = 16	8.4 (3.0) N = 15	9.3 (4.3) N = 21
	12 months	7.6 (2.1) N = 15	8.9 (3.0) N = 23	10.1 (5.5) N = 17

significantly higher baseline mUPDRS compared to those without OSA, adjusting for potential confounders. This higher baseline mUPDRS is consistent with previous reports, where PD patients with more severe OSA were also more likely to have greater motor dysfunction [14].

This association could be explained in several ways. First, PD may predispose to OSA. Neuronal degeneration in respiratory control centres may affect OSA severity. This has been observed in a rat model of PD, where the degeneration of tyrosine hydroxylase neurons in the substantia nigra pars compacta caused respiratory deficits [15]. Resulting deficits may lead to sleep-disordered breathing. Motor dysfunction in PD can also affect upper airway musculature, and levodopa can influence upper airway obstruction [16]. We recently reported that long-acting levodopa use at night was associated with reduced OSA severity in PD [17]. Moreover, pharyngeal muscles in PD patients show atrophic changes and increased neural degeneration when compared to controls [18]. These upper respiratory abnormalities related to progressing PD may contribute to OSA pathophysiology.

However, OSA may also, in turn, have adverse effects on PD. In support of this, large population studies have suggested that pre-existing OSA predisposes to PD [5]. Conversely, a multicenter study from the International RBD Study Group found OSA not to be a risk factor for subsequent development of PD among idiopathic RBD patients, although OSA scoring criteria were not standardized or defined and likely differed between centres, making conclusions on OSA less reliable [19].

Intermittent hypoxemia, a consequence of OSA, may increase the loss of dopaminergic neurons in brain areas implicated in PD, such as the substantia nigra, as dopamine pathways appear to be particularly vulnerable to ischemic-anoxic insults [20]. Recent work in an animal model found increased inflammation and oxidative stress in the substantia nigra in response to chronic intermittent hypoxia [21]. Damage to neuronal integrity in the locus coeruleus, another area implicated in PD which plays an important role in maintaining a protective effect against neurotoxic insults, has also been found in response to intermittent hypoxemia [22]. OSA-related sleep fragmentation also has detrimental effects on the brain. It has been implicated in decreased neuronal excitability in regions including the locus coeruleus [23]. Additionally, sleep fragmentation due to OSA could impair homeostatic effects of sleep. Sleep promotes clearance of cellular degradation products accumulated during waking periods, such as β-amyloid and α-synuclein. The latter is believed to be a key element in PD pathogenesis and neurodegeneration [24]. Perturbed sleep and resulting

accumulation of neurotoxic waste could increase degeneration of dopaminergic and other neurons in PD.

Our most notable finding is that CPAP treatment of OSA was associated with a significantly reduced rate of change in mUPDRS over 12 months compared to patients without OSA. (Fig. 1A). These findings support the concept that treatment of OSA conferred a protective effect from OSA-related exacerbation of PD motor impairment. OSA patients in our cohort had more severe hypoxemia and greater respiratory-related sleep disruption at baseline compared to those without OSA. Improvement in sleep quality and oxygen saturation with CPAP may contribute to the observed slowing of mUPDRS progression through decreasing potential downstream effects of these disturbances on the brain.

In our main model, the rate of change in mUPDRS for OSA + CPAP- over the 12-month follow-up (β = 0.39, 95% CI: 0.00 to 0.78) was comparable to OSA-. This was comparable to the expected rate of change previously reported in PD patients (0.42–0.50/month) [25]. Although this might suggest that OSA did not significantly affect the progression of PD motor dysfunction, several factors may make this conclusion unreliable. First, the OSA + CPAP- group had a higher average mUPDRS at baseline and each follow-up time compared to OSA-. PD progression is non-linear. The mUPDRS increases more slowly in more advanced PD [26], and striatal dopaminergic function deteriorates more slowly with more severe disease [27]. Given the higher baseline mUPDRS in OSA + CPAP-, the comparable rate of change in that group relative to OSA- may, in fact, suggest a more marked deterioration than expected, which conceivably might be attributable to OSA. Moreover, sample size and other limitations may have affected results.

We used TUG as another measure of motor dysfunction. The TUG assesses gait and balance, has been validated in PD and may be more representative of functional status than mUPDRS [28]. While there was no statistically significant difference between OSA + and OSA- in baseline TUG values, it is interesting to note that those who chose to use CPAP had higher baseline TUG scores indicating greater impairment. The change over time assessed using our mixed model is consistent with mUPDRS results, in that it suggests stabilization of TUG in CPAP-treated individuals, with a statistically significant difference as compared to OSA + CPAP-, though not OSA-. Differences in between-group significance between the two outcome measures (mUPDRS and TUG) may be explained by insufficient statistical power, and different distribution of missing data among patients (Table 2).

The restricted sample size is the main limitation of the study and was likely a factor in between-group comparison. Our models adjust for several confounders, which, with smaller sample sizes, may increase the risk of unreliable estimates. However, estimates from the unadjusted model were comparable to the main model. Additionally, we did not systematically perform PSG on therapeutic CPAP to confirm improvement in sleep architecture or hypoxemia. However current CPAP therapy is highly effective in alleviating OSA. Also, CPAP use was not consistent over time in individuals. The OSA + CPAP- group at 3 months included individuals who used CPAP for under 3 months. Hence there may be some residual effect of CPAP in the OSA + CPAP- group, and it is unknown whether any effect of CPAP on PD outcomes persists after discontinuation. Due to the limited sample size we chose not to exclude those individuals from our analyses. It is also unknown if there is a threshold effect for minimal number of hours of use per night for any beneficial effect. The OSA + CPAP- group may also have undertaken other interventions to improve their OSA. Furthermore, our study population is not completely representative of the entire PD population because we excluded patients who were unable to physically attend in-laboratory PSG, thus excluding advanced PD patients. OSA in our cohort occurred in 70.1% of participants. While this may seem greater than expected OSA prevalence in the general population and PD studies [29], it should be noted that ours was not a prevalence study. Participants were aware they would undergo a sleep study and hence those with sleep complaints may have self-selected preferentially. In addition, we have used the AASM "Chicago criteria" for respiratory event scoring, which are known to be more sensitive than other scoring criteria [13]. Nevertheless, our results confirm the relevance of this scoring method with respect to clinically important outcomes.

Our analysis builds on the current body of literature assessing the relationship between OSA and PD. A previous study has reported that OSA was associated with cognitive dysfunction and excessive daytime sleepiness [6]. CPAP therapy improved sleep architecture and decreased daytime sleepiness in a short trial [30] and also improved cognition and other non-motor symptoms in an observational study [7].
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To our knowledge, this is the first study reporting the effect of OSA and CPAP on motor symptom progression in PD. We have found that OSA is associated with greater motor dysfunction at baseline, and that treatment with CPAP is associated with attenuation of motor deterioration over time, measured by mUPDRS and TUG. We propose that the findings of this study support a pathophysiologic role for OSA in the progression of PD motor dysfunction. We therefore believe that further studies are warranted to more fully explore the mechanisms underlying the interaction between OSA and PD pathophysiology as well as the long-term impact of treating OSA on motor dysfunction and other key clinical outcomes in PD.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.12.001.

References

[1] O. Riedel, D. Bitters, U. Amann, E. Garbe, I. Langner, Estimating the prevalence of Parkinson's disease (PD) and proportions of patients with associated dementia and depression among the older adults based on secondary claims data, Int. J. Geriatr. Psychiatry 31 (2016) 938–943, https://doi.org/10.1002/gps.4414.

[2] K. Wirdefeldt, H.-O. Adami, P. Cole, D. Trichopoulos, J. Mandel, Epidemiology and etiology of Parkinson's disease: a review of the evidence, Eur. J. Epidemiol. 26 (2011) S1–S58, https://doi.org/10.1007/s10654-011-9581-6.

[3] Y.-P. Huang, L.-S. Chen, M.-F. Yen, C.-Y. Fann, Y.-H. Chiu, H.-H. Chen, S.-L. Pan, Parkinson's disease is related to an increased risk of ischemic stroke—a population-based propensity score-matched follow-up study, PLoS One 8 (2013) e68314, , https://doi.org/10.1371/journal.pone.0068314.

[4] C. Lal, C. Strange, D. Bachman, Neurocognitive impairment in obstructive sleep apnea, Chest 141 (2012) 1601–1610, https://doi.org/10.1378/chest.11-2214.

[5] N.-C. Yeh, K.-J. Tien, C.-M. Yang, J.-J. Wang, S.-F. Weng, Increased risk of Parkinson's disease in patients with obstructive sleep apnea: a population-based, propensity score-matched, longitudinal follow-up study, Medicine (Baltim.) 95 (2016) e2293, , https://doi.org/10.1097/MD.0000000000002293.

[6] V.P. Mery, P. Gros, A.-L. Lafontaine, A. Robinson, A. Benedetti, R.J. Kimoff, M. Kaminska, Reduced cognitive function in patients with Parkinson disease and obstructive sleep apnea, Neurology 88 (2017) 1120–1128, https://doi.org/10.1212/WNL.0000000000003738.

[7] M. Kaminska, V.P. Mery, A.-L. Lafontaine, A. Robinson, A. Benedetti, P. Gros, R.J. Kimoff, Change in cognition and other non-motor symptoms with obstructive sleep apnea treatment in Parkinson's disease, J. Clin. Sleep Med. 14 (2018) 819–828, https://doi.org/10.5664/jcsm.7114.

[8] A.J. Hughes, S.E. Daniel, L. Kilford, A.J. Lees, Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases, J. Neurol. Neurosurg. Psychiatry 55 (1992) 181–184.

[9] C.G. Goetz, B.C. Tilley, S.R. Shaftman, G.T. Stebbins, S. Fahn, P. Martinez-Martin, W. Poewe, C. Sampaio, M.B. Stern, R. Dodel, Movement disorder society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results, Mov. Disord. 23 (2008) 2129–2170.

[10] D. Podsiadlo, S. Richardson, The timed “up & Go”: a test of basic functional mobility for frail elderly persons, J. Am. Geriatr. Soc. 39 (1991) 142–148, https://doi.org/10.1111/j.1532-5415.1991.tb01616.x.

[11] C.L. Tomlinson, R. Stowe, S. Patel, C. Rick, R. Gray, C.E. Clarke, Systematic review of levodopa dose equivalency reporting in Parkinson's disease, Mov. Disord. 25 (2010) 2649–2653, https://doi.org/10.1002/mds.23429.

[12] R. Berry, R. Brooks, C. Gamaldo, The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications 2.3 Darien, IL, 2016.

[13] Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research, Sleep 22 (1999) 667.

[14] V. Cochen De Cock, M. Abouda, S. Leu, D. Oudiette, E. Roze, M. Vidailhet, T. Similowski, I. Arnulf, Is obstructive sleep apnea a problem in Parkinson's disease? Sleep Med. 11 (2010) 247–252, https://doi.org/10.1016/j.sleep.2009.05.008.

[15] M. Tuppy, B.F. Barna, L. Alves-Dos-Santos, L.R.G. Britto, S. Chiavegatto, T.S. Moreira, A.C. Takakura, Respiratory deficits in a rat model of Parkinson's disease, Neuroscience 297 (2015) 194–204, https://doi.org/10.1016/j.neuroscience.2015.03.048.

[16] W.G. Vincken, C.M. Darauay, M.G. Cosio, Reversibility of upper airway obstruction after levodopa therapy in Parkinson's disease, Chest 96 (1989) 210–212.

[17] P. Gros, V.P. Mery, A.L. Lafontaine, A. Robinson, A. Benedetti, R.J. Kimoff, M. Kaminska, Obstructive sleep apnea in Parkinson's disease patients: effect of Sinemet CR taken at bedtime, Sleep Breath. 20 (2016) 205–212, https://doi.org/10.1007/s11325-015-1208-9.

[18] L. Mu, S. Sobotka, J. Chen, H. Su, I. Sanders, C.H. Adler, H.A. Shill, J.N. Caviness, J.E. Samanta, T.G. Beach, Altered pharyngeal muscles in Parkinson disease, J. Neuropathol. Exp. Neurol. 71 (2012) 520–530, https://doi.org/10.1097/NEN.0b013e318258381b.

[19] B. Dawson, A. Pelletier, R.B. Postuma, L. Ferini-Strambi, M. Zucconi, M. Puligheddu, E. Antelmi, G. Plazzi, J. Santamaria, V. Cochen De Cock, C. Trenkwalder, D. Arnaldi, F. Nobili, B. Mollenhauer, F. Sixel-Doering, A. Videnovic, K. Sonka, P. Dusek, K.-Y. Jung, J.Y. Montplaisir, D. Kunz, F. Bes, Y. Dauvilliers, F. Provini, P. Cortelli, K. Ehgoetz Martens, S.J. Lewis, J. Buskova, M. Pavlova, A. Heidbreder, J.-F. Gagnon, Z. Gan-Or, A. Iranzo, C. Gaig, G. Mayer, S. Morbelli, C. Lo, M. Rolinski, M. Hu, T.R. Barber, A. Stefani, B. Högl, E. Holzknecht, P. Mahlknecht, A.R. Boeve, B.F. Boeve, E.K. St Louis, L.N. Teigen, G. Toscano, M. Terzaghi, R. Manni, A. Janzen, W.H. Oertel, I. Arnulf, S. Leu-Semenescu, Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study, Brain 142 (2019) 744–759, https://doi.org/10.1093/brain/awz030.

[20] M.J. Decker, D.B. Rye, Neonatal intermittent hypoxia impairs dopamine signaling and executive functioning, Sleep Breath. 6 (2002) 205–210, https://doi.org/10.1007/s11325-002-0205-y.

[21] B. Snyder, B. Shell, J.T. Cunningham, R.L. Cunningham, Chronic intermittent hypoxia induces oxidative stress and inflammation in brain regions associated with early-stage neurodegeneration, Phys. Rep. 5 (2017) e13258, , https://doi.org/10.14814/phy2.13258.

[22] Y. Zhu, P. Fenik, G. Zhan, E. Mazza, M. Kelz, G. Aston-Jones, S.C. Veasey, Selective loss of catecholaminergic wake active neurons in a murine sleep apnea model, J. Neurosci. 27 (2007) 10060–10071, https://doi.org/10.1523/JNEUROSCI.0857-07.2007.

[23] Y. Li, L.A. Panossian, J. Zhang, Y. Zhu, G. Zhan, Y.-T. Chou, P. Fenik, S. Bhatnagar, D.A. Piel, S.G. Beck, S. Veasey, Effects of chronic sleep fragmentation on wake-active neurons and the hypercapnic arousal response, Sleep 37 (2014) 51–64, https://doi.org/10.5665/sleep.3306.

[24] E. Masliah, E. Rockenstein, I. Veinbergs, M. Mallory, M. Hashimoto, A. Takeda, Y. Sagara, A. Sisk, L. Mucke, Dopaminergic loss and inclusion body formation in alpha-synuclein mice: implications for neurodegenerative disorders, Science 287 (2000) 1265–1269.

[25] W. Poewe, Clinical measures of progression in Parkinson's disease, Mov. Disord. 24 (2009) S671–S676, https://doi.org/10.1002/mds.22600.

[26] A. Schrag, R. Dodel, A. Spottke, B. Bornschein, U. Siebert, N.P. Quinn, Rate of clinical progression in Parkinson's disease. A prospective study, Mov. Disord. 22 (2007) 938–945, https://doi.org/10.1002/mds.21429.

[27] R. Hilker, K. Schweitzer, S. Coburger, M. Ghaemi, S. Weisenbach, A.H. Jacobs, J. Rudolf, K. Herholz, W.-D. Heiss, Nonlinear progression of Parkinson disease as determined by serial positron emission tomographic imaging of striatal fluorodopa F 18 activity, Arch. Neurol. 62 (2005) 378–382, https://doi.org/10.1001/archneur.62.3.378.

[28] S. Morris, M.E. Morris, R. Iansek, Reliability of measurements obtained with the Timed “Up & Go” test in people with Parkinson disease, Phys. Ther. 81 (2001) 810–818.

[29] T. Young, M. Palta, J. Dempsey, J. Skatrud, S. Weber, S. Badr, The occurrence of sleep-disordered breathing among middle-aged adults, N. Engl. J. Med. 328 (1993) 1230–1235, https://doi.org/10.1056/NEJM199304293281704.

[30] A.B. Neikrug, L. Liu, J.A. Avanzino, J.E. Maglione, L. Natarajan, L. Bradley, A. Maugeri, J. Corey-Bloom, B.W. Palmer, J.S. Loredo, S. Ancoli-Israel, Continuous positive airway pressure improves sleep and daytime sleepiness in patients with Parkinson disease and sleep apnea, Sleep 37 (2014) 177–185, https://doi.org/10.5665/sleep.3332.