Sleep breathing disorders in patients with idiopathic Parkinson’s disease

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Summary

Study objectives: to investigate the presence of sleep breathing disorders in patients with idiopathic Parkinson’s disease (PD) and their correlation with the severity of the disease.

Participants: Fifteen patients (mean age 63 ± 4 years) with idiopathic PD (Group A) and 15 healthy matched controls (Group B) were studied. All patients were under treatment with l-Dopa/Carbidopa and classified according to the UPDRS motor scale: 8 had mild disease (UPDRS < 12), 6 moderate (UPDRS: 12–22) and 1 severe (UPDRS > 22).

Measurements and results: All participants underwent full night polysomnography (PSG). The sleep-wake history was assessed. Spirometry, maximal respiratory pressures and arterial blood gases were also measured. Snoring was more common in Group A patients (73.3% vs. 33.3%, p = 0.002). Among the parameters studied apnea hypopnea index (AHI), mean O2 saturation, minimum O2 saturation, REM% sleep and Arousal Index (Arousal Index) were statistically different between the two groups. Furthermore, 9 PD patients fulfilled the criteria for obstructive sleep apnea-hypopnea syndrome (OSAHS) predominately mild, 1 for central sleep apnea hypopnea syndrome (CSAHS) and 5 were normal. In all patients a marked reduction in percentage REM sleep was observed. Among the patients with OSAHS 5 had mild PD, 3 moderate and 1 severe. The patient with CSAHS had moderate disease. Finally, 3 patients with mild and 2 with moderate PD had no evidence of sleep breathing disorders. Correlations between severity of disease and sleep parameters are provided.

Conclusion: Our results suggest that sleep breathing disorders, predominantly obstructive, seem to be common in PD and those events correlate with the severity of the disease.

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KEYWORDS
Parkinson’s disease; Sleep; Breathing disorders

Introduction

Parkinson’s disease (PD) is a degenerative neurological disorder characterized by akinesia, bradykinesia, rigidity, postural instability and tremor.1

Sleep disorders are common in idiopathic PD, being reported in 74–98% of patients, adversely affecting their quality of life.2–3 The most frequent sleep disorder in PD is sleep fragmentation with frequent and prolonged awakenings and excessive daytime sleepiness.4–5 Nocturia, difficulty in turning over in bed, tremor, leg cramps, vivid dreams/nightmares, rapid eye movement behavior disorder, back pain, limb/facial dystonia and leg jerks are common...
problems causing nocturnal awakenings in PD patients. There is also evidence that patients with PD die more frequently in the early hours of the day from respiratory "insufficiency" compared to patients with other neurological disorders, probably due to centrally mediated respiratory problems and upper airway obstruction caused by irregular glottic and supraglottic structures.4,14

There are few reports on breathing disorders during sleep in patients with idiopathic PD who present paroxysmal tachypnea, breath holding, irregular breathing and sleep apnea, whereas in a study in two patients with idiopathic PD no breathing disorders were revealed.7,14–17 There is one study in 10 patients with idiopathic PD (40% untreated) which included a patient exhibiting obstructive sleep apnea hypopnea syndrome (OSAHS).15 Furthermore, in another study in 54 patients with idiopathic PD, all levodopa treated, referred for excessive daytime sleepiness (EDS), 20% presented a moderate to severe OSAHS.18

The aim of this study was to assess the presence of sleep breathing disorders in patients with idiopathic PD under treatment and to examine if these disorders correlate with the severity of the disease.

Methods

Fifteen patients (12 males, 3 females) suffering from idiopathic PD diagnosed according to clinical manifestations were recruited (Group A). All patients presented tremor, bradykinesia and rigidity and had a distinct improvement after the administration of anti-parkinsonian therapy. Patients were recruited consecutively among those who attended the Neurological Department of the Hospital and no one declined participation. Additionally, 15 healthy controls matched regarding sex, age, smoking history and BMI with the Group A consisted the control group (Group B). The control group consisted of healthy participants randomly chosen who did not report any sleep complaints. The demographic characteristics of both groups, smoking history, BMI and severity of Parkinson’s disease are shown in Table 1. The distribution of the patients was not uniform, as only one patient with severe PD participated to the study. All PD patients were under treatment with carbidopa/levodopa individualized doses. The severity of Parkinson’s disease was classified according to the unified Parkinson’s disease rating scale (UP-DRS)—motor scale evaluating the following parameters related to motor activity: speech, facial expression, tremor at rest, action or postural tremor of hands, rigidity, finger taps, movements showing reduction in amplitude, rapid alternating movements of hands, legs agility, arising from the chair, posture, gait, postural stability and body bradykinesia and hypokinesia (Table 1).20 Exclusion criteria for all participants were: history of lung disease that might have led to structural or functional pulmonary dysfunction, obesity, heart diseases, other neurological diseases and endocrinological disorders. All participants underwent physical examination and a medical history was taken. In addition spirometry was performed and arterial blood gases and maximum inspiratory (MIP) and expiratory (MEP) pressures were measured. Maximum inspiratory and expiratory mouth pressures (MIP and MEP) were measured at FRC and TLC respectively, during maximum efforts against a closed airway using a respiratory muscle pressure meter (Forth Institute Structure ad Laser). The best of three maneuvers sustained for at least 1 s was selected for analysis. Reference values for MIP and MEP were taken from Black and Hyatt.21 Spirometry and flow-volume loop were recorded using a Jaeger flowmeter (Wuerzburg, Germany), forced vital capacity(FVC) and forced expiratory volume (FEV1) in 1 s were measured according to standard methods.22 Both spirometry and maximum pressures were performed one hour after the administration of the individualized dose of L-Dopa/Carbidopa (peak dose according to the pharmacokinetics of the drug).23

Participants underwent a full night polysomnography (PSG) in the sleep laboratory. Monitoring started at 10:30 pm and ended at 06:30 am. Recordings were made with an Alice-4 18 channel polygraph (Alice-4 Respiromics, Pittsburgh, Pennsylvania, USA) and included monitoring of electroencephalogram (C3/A2, C4/A1 and C2/OZ), electrooculogram, genioglossus and anterior tibialis electromyograms, oxygen saturation, nasal thermistors and nasal canula pressure transducer, thoracic and abdominal bands, microphone for snoring and body position electrode (all according to the 10–20 international electrode placement system).24

Sleep staging was scored visually according to the criteria of Rechtschaffen and Kales24 and microarousals were defined according to the criteria of Bonnette et al.25 Respiratory events analysis and apnea hypopnea index was scored visually and calculated according to international criteria with hypopnea manifesting as an adverse of thoracoabdominal effort of at least 50% with an associated oxygen desaturation of at least 4% and apnea as a cessation of airflow at the nose and mouth lasting at least 10 s and were classified as obstructive or
central on the basis of the presence of paradoxical movements of the rib cage of the abdomen.\textsuperscript{26} OSAHS was defined as mild, moderate or severe when AHI was between 5.1 and 15, 15.1 and 30, and greater than 30 respectively.

All participants signed a consent form approved by the Crete University Ethics Committee.

Statistical analysis

SPSS 10.0 package for windows was used for statistical analysis. Since the distribution of values of sleep and respiratory parameters of subjects of both groups were not normal we used the Mann–Whitney test for comparison of differences between the two groups. Values are shown as mean and median. A \( p \)-value less than 0.05 was considered as significant. In order to explore the correlation between severity of PD (UPDRS) with AHI, AI and median SatO\(_2\) in PD patients (group B) we performed a logarithmic (log(10)) transformation of the above parameters in order to achieve a normal distribution of values and therefore to enable the use of parametric correlation (Pearson and multiple regression) tests.

Results

Respiratory parameters

On average the FEV\(_1\), FVC, FEV\(_1\)/FVC predicted were within normal limits in both groups. The median values of MIP and MEP in PD patients were 55% pred and 45% pred, respectively, while normal controls they were 83.5% pred and 79% pred respectively (\( p < 0.0000 \)). MIP and MEP were not significantly correlated to FEV\(_1\), FVC and FEV\(_1\)/FVC.

The arterial blood gases were within normal limits in all participants. Table 2 presents a summary of the measured respiratory parameters in both groups.

Sleep parameters

The median rapid eye movement (REM) sleep time was 9.0% of the total duration in PD patients and 16.0% in healthy controls (\( p = 0.005 \)). Patients presented frequent awakenings and the median Arousal Index (AI) was 21.0/h, while in healthy controls AI it was 9.9 (\( p = 0.0002 \)), showing that sleep fragmentation in PD patients is almost 2.12 times higher compared to normal controls. The median frequency of leg movements during sleep was 5.9/h in PD patients and 3.2/h in healthy controls (\( p = 0.009 \)) (Table 3).

Sleep breathing parameters

Snoring

Eleven (73.3%) of the patients were snorers. Among healthy controls 5 (33%) were habitual snorers and 3 snored occasionally.

Apnea/hypopnea events

Five patients (33.3%) had a normal pattern of breathing during sleep, whereas 11 (73.3%) presented some type of sleep breathing disorders (Fig. 1). All patients who exhibited sleep breathing disorders complained of daytime sleepiness,

Table 1  Demographic characteristics of subjects.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>M/F</td>
<td>12/3</td>
<td>12/3</td>
</tr>
<tr>
<td>BMI</td>
<td>27 ± 1.3</td>
<td>27 ± 1.2</td>
</tr>
<tr>
<td>Age ± SD (yrs)</td>
<td>63 ± 4</td>
<td>60 ± 4</td>
</tr>
<tr>
<td>Duration of Parkinson’s disease (yrs)</td>
<td>6 ± 5</td>
<td>7 ± 5</td>
</tr>
<tr>
<td>Smoking history</td>
<td>Smokers</td>
<td>5 (mean pack years: 70.0 ± 21.6)</td>
</tr>
<tr>
<td></td>
<td>Non-smokers</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Ex smokers</td>
<td>3</td>
</tr>
<tr>
<td>Disease severity (UPDRS)</td>
<td>Mild (UPDRS &lt; 12)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Moderate (12 ≤ UPDRS ≤ 22)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Severe (UPDRS &gt; 22)</td>
<td>1</td>
</tr>
</tbody>
</table>

Group A: Parkinson’s disease patients. Group B: Controls.
choking or gasping during sleep, daytime fatigue, unrefreshing sleep and recurrent awakenings from sleep. The Epworth Sleepiness Scale was 12.3 for the patients, while for the control group it was 6.1 ($p = 0.0014$). The median AHI was 11.0 for PD patients and 5.7 for healthy controls ($p = 0.048$), the median $O_2$ saturation during sleep was 93.0% for patients and 96% for healthy controls ($p = 0.0003$), while the median lowest $O_2$ saturation was 90.0% for patients and 92% for healthy controls ($p = 0.002$). All measured parameters have been adjusted to their BMI. Among the 10 patients who exhibited sleep breathing disorders, 9 fulfilled the criteria for moderate obstructive sleep apnea hypopnea syndrome (OSAHS) (apneas: 15.1–30/h) and one patient suffered from central sleep apnea hypopnea syndrome (CSAHS).

### Table 2  Comparison of respiratory parameters between groups.

<table>
<thead>
<tr>
<th>Sleep parameter</th>
<th>Group A ($n = 15$)</th>
<th>Group B ($n = 15$)</th>
<th>$p^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV$_1$ (%) pred</td>
<td>89</td>
<td>90.4</td>
<td>0.9</td>
</tr>
<tr>
<td>FVC (%) pred</td>
<td>93</td>
<td>95.6</td>
<td>0.73</td>
</tr>
<tr>
<td>FEV$_1$ / FVC pred</td>
<td>94</td>
<td>95.2</td>
<td>0.59</td>
</tr>
<tr>
<td>MIP (%) pred</td>
<td>62</td>
<td>82</td>
<td>&lt;0.0000</td>
</tr>
<tr>
<td>MEP (%) pred</td>
<td>41</td>
<td>79</td>
<td>&lt;0.0000</td>
</tr>
<tr>
<td>$P_{O_2}$ (mmHg)</td>
<td>80</td>
<td>83</td>
<td>0.98</td>
</tr>
<tr>
<td>$P_{CO_2}$ (mmHg)</td>
<td>42</td>
<td>39</td>
<td>0.97</td>
</tr>
<tr>
<td>pH</td>
<td>7.4</td>
<td>7.4</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Group A: Parkinson's disease patients. Group B: Controls.

$^a$Mann-Whitney test.

### Table 3  Comparison of sleep variables between groups.

<table>
<thead>
<tr>
<th>Sleep parameter</th>
<th>Group A ($n = 15$)</th>
<th>Group B ($n = 15$)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snoring (%) patients</td>
<td>73.3</td>
<td>33.3</td>
<td>0.002$^a$</td>
</tr>
<tr>
<td>TST (h)</td>
<td>5.9</td>
<td>5.8</td>
<td>0.8$^b$</td>
</tr>
<tr>
<td>REM %</td>
<td>10.8</td>
<td>16.4</td>
<td>0.005$^b$</td>
</tr>
<tr>
<td>AHI (NL: 0–5)</td>
<td>12.2</td>
<td>5.7</td>
<td>0.048$^b$</td>
</tr>
<tr>
<td>Median SaO$_2$</td>
<td>92.5</td>
<td>95.8</td>
<td>0.0003$^b$</td>
</tr>
<tr>
<td>Minimum SaO$_2$</td>
<td>88.5</td>
<td>92.1</td>
<td>0.002$^b$</td>
</tr>
<tr>
<td>Al</td>
<td>24.1</td>
<td>9.9</td>
<td>0.0002$^b$</td>
</tr>
<tr>
<td>Leg movements (/h)</td>
<td>5.4</td>
<td>3.3</td>
<td>0.009$^b$</td>
</tr>
</tbody>
</table>


$^a$Chi-square test.

$^b$Mann-Whitney test.

Figure 1  Relationship between severity of Parkinson’s disease and sleep breathing disorders.
Figure 1 shows the distribution of the PD patients according to their breathing pattern during sleep and the severity of PD. Among the patients with OSAHS, 5 had mild PD, 3 moderate PD and 1 severe PD. The patient with CSAHS had moderate PD. Among the patients with no evidence of sleep breathing disorders, 3 had mild PD and 2 moderate PD.

In Table 4 it is shown that the logarithmically transformed values of UPDRS correlated significantly with the logarithmically transformed values of AHI, AI and median SatO2. The correlation remained significant after adjustment for age in a multiple regression model (partial correlations and p values are also shown in Table 4). In the same table it is shown that there was a statistically significant correlation between logarithmically transformed AHI and logarithmically transformed AI before and after adjustment for age. Results of the sleep study and correlations between severity of disease and sleep parameters are shown in Tables 5 and 6, respectively.

Discussion

A number of studies have shown that the most common sleep disorder in PD patients is difficulty of maintaining sleep, as a result of sleep fragmentation.6-8,10,11,16,27 Sleep fragmentation is also common in age-matched control groups but PD patients wake up more frequently suggesting that the disease itself plays a more important role than age. Furthermore frequent awakenings appear to be related to the disease process.6,8,14,18 The results of this study showing frequent awakenings in PD patients with an AI approximately high are in agreement with previous reports.6-8,10,11,16,18,27-30

Frequent nocturia, nocturnal akinesia and other kinetic dysfunctions as dystonias, cramps, pains,6-8 increased muscle activity,31 depression10 and declining efficacy of dopaminergic agents27 have been reported as causes for the sleep fragmentation in PD. In the current study the significant correlation between AHI and AI suggests that many of the arousals are strongly associated with the high incidence of apnea/hypopnea events whereas kinetic dysfunctions contribute less to the sleep fragmentation.

The TST and REM sleep are usually decreased in PD patients. In our study TST was slightly reduced (median TST: 6.0 h), while in other studies TST varies from 4.2 to 4.89 h15-16 with some reports finding that TST was within the normal range.6,18-19

In this study REM sleep was reduced with median REM (%) comprising 9.0% of the TST. This is in agreement with previous reports showing values ranging from 8.5% to 20%.3-6,15-17,19,28-29 Several conditions such as depression, frequent awakenings due to motor deficits, levodopa, dopaminergic agonists causing hallucinations, selegeline, benzodiazepines, amitriptyline and the first-night effect of the sleep study have been suggested as causes of the reduction of REM% and TST.5-6,16,29

The main finding of our study was the high incidence of apneic syndromes that were detected in patients with PD. To our knowledge, only isolated cases of obstructive and central sleep apneas have been previously reported in PD patients without fulfilling the criteria of sleep apnea syndromes.7,11,19 Two studies suggested a high incidence of mainly obstructive and few central apneic episodes: the first one presents one patient (5%) with OSAHS in 20 idiopathic and postencephalitic PD patients15 and the second one found that 20% of 54 PD patients who were referred due to excessive daytime sleepiness (EDS) had AHI greater than 15/h indicating OSAHS.18 In previous studies it has been found that some patients with idiopathic PD and parkinsonism presented upper airway obstruction(UAO) and abnormal flow/volume loops, which may be related to the high incidence of apnea/hypopnea events that were detected in the current

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Correlations between logarithmically transformed sleep parameters in univariate (Pearson’s) and multiple regression (after adjustment for age) models.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate correlation</td>
<td>Multiple regression after adjustment for age</td>
</tr>
<tr>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>LogUPDRS vs. LogAHI</td>
<td>0.67</td>
</tr>
<tr>
<td>LogUPDRS vs. LogAI</td>
<td>0.58</td>
</tr>
<tr>
<td>LogUPDRS vs. Logmedian O2 Sat</td>
<td>0.66</td>
</tr>
<tr>
<td>LogAHI vs. LogAI</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Although in the current study, due to exclusion of subjects with anatomical and functional pulmonary diseases, pulmonary function tests were close to normal in both groups, in spite the fact that there was a considerable proportion of smokers among the recruited subjects a severe reduction of MIP and MEP was found suggesting abnormalities of respiratory muscle function. This corroborates previous studies showing evidence of muscular dysfunction at the level of the glottic and supraglottic structures with irregular jerky movements during endoscopic evaluation.

Additionally, in our study there was a significant correlation between the severity of PD and the severity of sleep breathing disorder. Sleep breathing disorders expressed by AHI and clinical symptoms are correlated to the severity of PD evaluated by the UPDRS. Patients with mild PD present either none or mild OSAHS, whereas patients with moderate to severe PD suffer from more severe OSAHS with higher AHI and more serious clinical symptoms. This is in agreement with a previous study relating the incidence of apneic episodes with the severity of the disease.

In conclusion, our results suggest that patients with idiopathic PD seem to exhibit a high incidence of sleep breathing disorders, predominantly obstructive. In addition, a significant correlation between the severity of the disease and the severity of sleep breathing disorders was found.

Finally, the results of the present study suggest that sleep studies should be performed in patients with PD especially those presenting symptoms associated with sleep, in order to verify the presence of sleep breathing disorders.

References