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Risk of sleep-disordered breathing in Parkinson's disease

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Abstract

Objective—The objective of this study is to assess the risk of sleep-disordered breathing (SDB) in patients with Parkinson's disease (PD) in a cross-sectional survey of PD subjects and controls in a university-based movement disorders clinic.

Methods—One hundred thirty-four consecutive PD subjects and 94 control subjects without prior diagnosis of SDB were assessed. Participants were assessed with clinical history, Unified Parkinson's Disease Rating Scale, Geriatric Depression Scale, Berlin Questionnaire to classify SDB risk, Epworth Sleepiness Scale, Parkinson's Disease Sleep Scale, and SF-36 to examine quality of life. The presence of risk for SDB was assessed by the Berlin Questionnaire.

Results—High risk for SDB was apparent in 66 (49.3%) of the PD patients and 32 (34.8%) of the controls. After adjustment for age, gender, and body mass index (BMI), PD subjects in comparison to controls showed higher risk for SDB (odds ratio=2.81; 95% confidence interval, 1.36–5.82). Quality of life (physical component score) was significantly diminished in PD patients at high risk for SDB. PD severity did not correlate well with SDB risk. PD patients at high risk for SDB had higher BMIs and Epworth scores.

Conclusions—PD patients have features suggesting increased risk for SDB. This frequently undiagnosed sleep disorder may have a substantial impact on quality of life of PD patients.

Keywords

Sleep-disordered breathing; Obstructive sleep apnea; Parkinson's disease; Berlin questionnaire; Sleepiness; Depression; Quality of life

Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder affecting approximately 300 per 100,000 in industrialized nations [1–3]. Although PD is defined by motor dysfunction, PD is characterized also by a range of non-motor features such as dementia, psychiatric problems, autonomic dysfunction, and sleep disorders. Non-motor features are recognized as major sources of disability and impaired quality of life for PD patients [4–8]. Variables that most strongly predict disease-related disability and impaired quality of life are depression, impaired cognition, and insomnia [9,10]. Sleep problems are reported in 74–98% of PD patients, and sleep problems start early in the disease course [8,11–17]. The most frequent complaints are sleep fragmentation and excessive daytime sleepiness [18,19]. Recent studies of PD suggest high prevalence of a treatable sleep disorder, sleep-disordered breathing (SDB). The reported frequency of SDB in PD varies from 20% to 60%, perhaps due in part to disparities in study subject selection [20–23]. The high apparent frequency of SDB in PD is surprising as PD subjects often lack obesity, a major risk factor for SDB [24,25]. Upper airway anatomy alone may not explain SDB in PD. Upper airway patency, for example, is regulated by brain serotonergic neurons, which are known to degenerate in PD [26–29]. Alternative explanations for SDB in PD could include deficient respiratory muscle coordination [30] or autonomic dysregulation [31].

Existing frequency estimates of SDB in PD have limitations. A case–control retrospective polysomnographic (PSG) analysis of 49 PD subjects found that 43% suffered from SDB [22]. Another small study of 15 PD patients reported a higher frequency of SDB, approximately 60%, and SDB severity seemed to correlate with the severity of PD [21]. In a systematically evaluated series of 54 PD subjects with excessive daytime somnolence, 20% had PSG evidence of SDB [20]. However, selection of patients for PSG on the basis of sleepiness may lead to overestimation of the overall frequency of SDB in PD. Schafer [23] reported a series of 83 unselected subjects with parkinsonism, the great majority with PD, and found more than 50% had evidence of SDB. Cohen de Cock et al. [32] recently describe a lower incidence of SDB (27%) in an unselected series of 100 PD subjects (50 with excessive daytime sleepiness, 50 without) than in age-, gender-, and body mass index-matched controls (40%). The control population in this study, however, consisted primarily of hospital inpatients with suspected venous thromboembolism and a high prevalence of cardiopulmonary disease.

There is also a question as to the significance of PSG findings in PD patients. The majority of the subjects in the study of Diederich et al. [22] had only mild SDB (apnea/hypopnea index (AHI), 5–15). Similarly, the majority of subjects in the study of Cohen de Cock et al. [32] had mild to moderate SDB. In Schafer's series, only half of the PD subjects (25% of all PD subjects) with PSG evidence of SDB requiring treatment [23].

The main goal of this study was to survey sleep symptoms in a larger, more representative sample of PD patients, with an emphasis on SDB. Laboratory-based quantification of SDB in a sample of many older participants was not considered feasible. Instead, we administered several well-validated survey instruments commonly used in studies of PD and SDB. We also administered a standard quality of life instrument to survey possible impact of SDB on quality of life in PD.

Methods

Subjects

All subjects were recruited from the Movement Disorders Clinic of the University of Michigan, Ann Arbor, MI, USA. All study procedures were approved by the University of

Michigan IRB. Consecutive PD subjects meeting inclusion and exclusion criteria were approached about study participation. Fewer than 10% of approached subjects declined to participate. One hundred and thirty-four consecutive PD patients were recruited from September 2007 to February 2008. We studied 92 controls. Controls were non-blood relatives: spouses, other family members, caregivers, or another person who accompanied PD participants to visits. Subjects were excluded with (1) greater than mild to moderate dementia—Mini-Mental State Examination (MMSE) <16, (2) had an illness or condition other than PD with a lasting influence on brain function, (3) history of alcohol dependency, (4) history of other substance dependency, (5) currently abusing recreational drugs, or (6) active treatment with continuous or bilevel positive airway pressure or surgical treatment for SDB. Diagnosis of PD was based on the UK PD society Brain Bank diagnostic criteria [33].

Evaluations

PD and control participants were evaluated by one of two investigators (WC or PD) in a face-to-face interview after routine clinic visits. Degree of parkinsonism was evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS) [34]. Collection of information on demographic variables, SDB risk, quality of life, and sleep-related profiles took approximately 30–40 min.

Risk for SDB was evaluated with two questionnaires. The first is the self-administered Berlin Questionnaire (BQ), consisting of ten symptom-items in three categories related to the risk of having SDB [35]. Scoring stratifies subjects into high- and low-risk groups: a subject at high risk for SDB must have positive scores in two or more categories. Subjects who denied frequent symptoms, did not report symptoms, or scored positive for only one category were placed in the low-risk group. The BQ is used widely in research as a screen for SDB. High SDB risk on the BQ predicts PSG-proven SDB with a sensitivity of 86% and a specificity of 77% [35]. We also used the self-administered STOP questionnaire, which contains four items that assess snoring, tiredness/sleepiness, observed cessation of breathing during sleep, and blood pressure [36]. Results of the STOP also were used to divide subjects into high- and low-risk groups.

To assess generic quality of life, we used the SF-36, an instrument with good reliability, validity, and reproducibility, and history of use in studies of both PD and SDB [37–41]. The SF-39 is a multi-purpose, “short-form” health survey with 36 question-items that reflect eight dimensions of quality of life. Each dimension is reported on a norm-based scale of 0 to 100 with higher scores reflecting better quality of life. These dimensions represent multiple operational indicators of health, including behavioral function and dysfunction, distress and well-being, objective reports and subjective ratings, and both favorable and unfavorable self-evaluations of general health status. The dimensions are summarized by two main component scores, one for physical and the other for mental domains.

Sleep and related issues were examined with the Epworth Sleepiness Scale and the Parkinson's Disease Sleep Scale (PDSS). The Epworth Sleepiness Scale assesses subjective sleep propensity. Summed, total scores range from 0 to 24, and scores ≥ 10 suggest excessive daytime sleepiness [42]. The self-administered PDSS addresses 15 symptoms associated with sleep disturbance in PD. Each symptom is scaled from 0 (severe) to 10 (no symptom). The maximum cumulative score is 150 (symptom free) [43]. PDSS scores in PD are significantly different from control scores. Advanced PD subjects exhibit worse scores than those with milder disease [43].

Depression was evaluated with the short-form Geriatric Depression Scale (GDS-15) [44]. Cognitive impairment was assessed by the MMSE [45].

Statistical analysis

The data were entered by an investigator into a Microsoft Office Excel 2003 database and re-entered for verification. Statistical evaluations were carried out using SPSS version 14.0 for Windows (SPSS Inc, Chicago, IL, USA) and SAS (SAS Institute, Cary, NC, USA). The PD and control subjects or PD patients with high and low risk were compared for categorical variables using χ^2 tests and on continuous variables using Student's t tests. Mann–Whitney U tests were used when the outcome variables assumed ordinal values. Logistic regression or general linear models, as appropriate, were used to identify group differences on the Berlin, STOP, or SF-36 instruments. A p value less than 0.05 (two-tailed) was considered significant.

In a large US sample, the BQ identified about 40% of the subjects as having high risk for obstructive sleep apnea (OSA) [35]. A two-group Chi-square test with a 0.05 two-sided significance level has 81% power to detect the difference between a group with usual OSA risk (p_1) of 0.4 and another group with elevated OSA risk (p_2) of 0.6 (odds ratio (OR) of 2.250) if the sample size in each group is 100. This sample size provides 99% power to detect a 20%-point difference in the vitality subset scale of the SF-36 for the two groups. Target sample sizes were therefore 100 PD patients and 100 non-PD controls.

Results

SDB risk in PD vs. control subjects

Patients with PD were recruited more quickly than controls, and recruitment was terminated after controls reached $n=92$ and PD patients had been over sampled to compensate ($n=134$; Table 1). Age and gender differed between PD and control subjects, but body mass index did not. In addition, the proportion of subjects with obesity (body mass index ≥ 30) among PD patients (26.9%) and controls (30.4%) did not differ ($p=0.66$). The PD patients more frequently had high risk for SDB on the BQ, lower quality of life, lower mean MMSE scores, and higher GDS-15 scores. The PD patients showed lower (less desirable) PDSS total scores and higher Epworth Sleepiness Scale scores than controls. In contrast to BQ results, STOP scores did not differ significantly between groups ($p=0.14$).

Snoring was found in 89 (66.4%) of the PD patients and 57 (62.0%) of the controls ($p=0.58$). Observed apneas were reported with similar frequency in PD patients and controls (29 (21.6%) and 16 (17.4%), respectively). Daytime sleepiness was detected by the BQ in a higher proportion of PD patients than controls (50 (37.3%) vs. 17 (18.5%), $p=.004$).

In logistic regression models that accounted for age, gender, and body mass index, PD in comparison to control subjects more frequently showed high SDB risk on the BQ (OR=2.81; 95% confidence interval (CI), 1.36–5.82). A similar result was obtained with the STOP questionnaire (OR=2.15; 95% CI, 1.11–4.16).

Comorbidity in PD patients with high risk for SDB

To assess possible adverse effects of SDB, we compared PD subjects with high-risk and low-risk BQ scores. The PD subjects with high-risk vs. low-risk BQ scores showed increased depression on the GDS-15, sleepiness on the Epworth, and sleep disturbance on the PDSS (Table 2). PD patients with high vs. low BQ scores were younger and had higher body mass index.

SDB risk as a function of PD severity

Among the 134 PD patients, Hoehn and Yahr (H&Y) staging showed that 48 had early PD (H&Y stage 1 and 2) and 86 had advanced PD (H&Y stage 2.5, 3, 4, and 5; Fig. 1). A mild

tendency for more advanced PD to exhibit high-risk BQ scores did not reach significance ($p=.15$, Fig. 2). Patients with high-risk vs. low-risk BQ scores had higher mean UPDRS scores in the activities of daily living subscale (high vs. low risk, 11.3 ± 7.1 vs. 8.6 ± 5.1 , $p=0.01$) and total score (high vs. low risk, 37.8 ± 19.4 vs. 31.2 ± 15.3 , $p=0.03$; Fig. 3).

Quality of life in PD and relation to SDB risk

The PD patients in comparison to controls had lower quality of life, as reflected by each of the SF-36 subscales (Table 1 and Fig. 4). Within the PD group, statistically significant associations were observed between high BQ scores and worse results for several SF-36 subscales, including physical function, role physical, general health, vitality, mental health, and the overall physical component (Fig. 5). The contribution of SDB to the overall quality of life decrement associated with PD, in comparison to controls, was estimated. In a general linear model, PD severity, cognitive impairment, age, and gender together explained 20.7% of the variance in the physical component of the SF-36. Adding BQ results to this regression increased the variance explained to 23.0%. Therefore, presence or absence of symptoms suggestive of SDB accounted for $(23.0 - 20.7)/23.0 = 0.1$ or 10% of the quality of life difference between PD subjects and controls.

Discussion

This survey of PD patients and aged controls suggests increased risk for SDB in PD, in the range of twofold increase, even after controlling for potential confounding variables. This study is the first to our knowledge to show in PD patients that high risk for SDB is associated with augmented symptoms of depression and diminished quality of life. High risk for SDB in our subjects was associated only modestly with the severity of PD. Although limitations of this study included reliance on subjective reports, strengths included use of well-validated instruments, one of the largest PD samples characterized for both sleep and health covariates, and use of a reasonably well-matched group of aged control subjects. Our findings have implications for potential mechanisms of SDB, and for clinical approaches to sleep, sleep disturbance, and daytime sleepiness in PD patients.

The BQ was designed for use in primary care populations, where high risk of SDB is identified in 26.3–37.5% of patients surveyed [35,46]. When standard polysomnograms have been carried out on sample groups, the BQ has demonstrated a sensitivity of 0.86 and specificity of 0.77 for identifying patients with more than five respiratory events per hour. The BQ has a positive predictive value of 0.89 and a likelihood ratio of 0.97 [35]. Underdiagnosis of SDB is common in clinical practice. A large community-based study found that 93% of women and 82% of men with moderate to severe SDB had not been diagnosed previously [47]. The BQ is brief and easy to administer and might be considered for routine use in PD clinics.

Associations between SDB *or* PD and diminished quality of life have been demonstrated in a number of studies. Previous work showed, for example, that PD patients have poorer quality of life than controls, in proportion to increasing disease severity [48,49]. No prior study has demonstrated a relationship between SDB risk and quality of life in PD patients. Symptoms of depression, one of the most consistent determinants of reduced quality of life in PD [5], were more prominent in our study among patients at high risk for SDB than among those at low risk. Increased depressive features may be a mechanism by which SDB degrades quality of life in PD.

Additional interesting points emerge from our study in comparison with prior studies. Some previous studies reported that PD patients tend to have lower body mass index than controls [24,25]. One prior study suggested that at early or middle stages of PD, non-obese PD

patients frequently had rates of apneas and hypopneas consistent with SDB [22]. Our study, however, found that SDB symptoms were more frequent in PD patients with higher body mass indices. Snoring is considered a marker for OSA and, in some cases, may be a precursor of clinically significant sleep apnea [50]. Data from a small case-control study suggested that 73% of PD patients are snorers [22]. Our study confirmed this finding. Our finding furthermore that SDB risk in PD is associated with obesity suggests that mechanical factors affecting airway patency are still likely to be important in the genesis of SDB in PD. Mechanical, obesity-related influences may interact with central nervous system changes to increase risk for SDB in PD. One prior report found a significant correlation between PD severity and SDB occurrence [21]. Our data, however, suggested only a modest relationship between PD severity and high risk of SDB.

The PDSS has been proposed as a useful screening tool for sleep disturbances in PD patients [43]. Data from our study showed that PDSS scores in PD subjects with high risk for SDB were significantly worse than those with low risk for SDB. This suggests that the PDSS is sensitive to SDB-related features, but the difference in PDSS scores between high and low-risk PD groups was modest. The PDSS contains no questions directly pertinent to SDB screening (e.g., snoring and witnessed apneas), which may be a limitation of the instrument. The PDSS is helpful in identification of several sleep conditions such as sleep maintenance insomnia, restless leg syndrome, or para-somnias. Supplementing the PDSS with the BQ, STOP, or other similar instrument may provide a more comprehensive screen for sleep disorders in PD.

Several limitations of this study deserve consideration. Selection bias may have arisen due to mismatch between PD patients and controls. This study was not designed to produce epidemiological data on the prevalence of SDB or to estimate the diagnostic utility of the BQ in the PD population. In particular, we used spouse or caregiver controls. Our control group was younger than our PD subjects. In addition, as is typical for PD populations, a majority of our PD subjects were men, and correspondingly, a majority of control subjects were women. SDB is more significantly more common in men than women, which could confound study results [51,52]. Redline et al. suggested that women are less likely to report typical snoring symptoms or overt apnea than men [53]. Given that overt apnea is a major criterion on the BQ and STOP, this is another potential gender-related confound. Young et al., however, did not discover any differences in classic symptoms between genders, and the issue of gender differences in symptoms remains controversial [52,54]. We adjusted, however, for both age and gender with logistic regression and still found high SDB risk on the BQ in PD subjects. The BQ includes questions about snoring. Without information from a bed partner, snoring data may be incomplete. The BQ also includes questions about sleepiness, and therefore, associations between BQ results and other measures of sleepiness, such as the Epworth, may be in part artificial. PD itself and related medical management could potentially augment daytime sleepiness and contribute to false positive BQ results. Sleep disturbances and excessive daytime somnolence in PD are likely to result from a combination of disease-related and treatment-related phenomena [20]. Medications used to treat PD, for example, have significant effects on sleep/wakefulness mechanisms and may produce excessive daytime somnolence [55]. While the BQ is a well-validated screening instrument, our results do not definitively identify PD subjects with SDB nor does the BQ differentiate mild to moderate SDB from severe SDB.

Nonetheless, our data from one of the largest PD samples with matched comparison subjects build on existing evidence to show that PD patients carry increased risk for SDB and suggest, for the first time, that SDB could account for a significant fraction of diminished quality of life in PD. Appropriate awareness, identification, and management of SDB could have significant impact on sleepiness, depression, quality of life, and general health for these

patients. Future research is warranted to establish the diagnostic utility of SDB screening in PD patients with systematic validation by polysomnography, assessment of SDB severity, and to determine whether treatment of SDB might improves sleepiness, depression, quality of life, and general health status in PD.

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Fig. 1. Distribution of disease stage in 134 Parkinson's disease (PD) patients (based on modified Hoehn and Yahr staging). y-axis, numbers of patients; x-axis, Hoehn and Yahr PD stage

Fig. 2. Berlin Questionnaire outcome (high vs. low sleep-disordered breathing risk) and Parkinson's disease (PD) stage in PD patients. *y*-axis, numbers of PD patients; *x*-axis, PD Hoehn and Yahr stage

* $p < .05$ high vs. low SDB risk (on Berlin Questionnaire)

Fig. 3. Berlin Questionnaire outcome (high vs. low sleep-disordered breathing (SDB) risk) and Unified Parkinson's Disease Rating Scale (UPDRS) in Parkinson's disease subjects. y-axis, UPDRS score; x-axis, high- and low-risk SDB categories and UPDRS subscores and total scores

Fig. 4.

SF-36 results for Parkinson's disease (PD) patients and controls (mean ± SD, with population norm of 50 ± 10). y-axis, score (100, best health; 0, poorest health); x-axis, SF-36 subscales; * $p < .05$; ** $p < .001$, PD patients vs. controls

Fig. 5.

SF-36 results for Parkinson's disease patients only, split into those with and without high risk for sleep-disordered breathing on Berlin Questionnaire. y-axis, score (100, best health; 0, poorest health); x-axis, SF-35 subscales; * $p < .05$, ** $p < .001$, high risk vs. low risk (Berlin Questionnaire)

Table 1

Characteristics of Parkinson's disease patients and controls (mean $\pm$ SD, number of subjects, or number (column percent))

	PD subjects (n=134)	Controls (n=92)
Age (years)	70.7 $\pm$ 10.0**	64.5 $\pm$ 9.9
Gender (no. male/no. female)	88/46**	25/67
PD severity (no. mild (stage 1–2)/no. severe (stage 2.5–5))	48/86	n/a
Body mass index (kg/m ²)	26.8 $\pm$ 5.5	27.5 $\pm$ 5.8
Mini-Mental Status Exam (MMSE)	27.6 $\pm$ 2.8**	29.3 $\pm$ 1.3
Epworth Sleepiness Scale	9.9 $\pm$ 5.6*	5.8 $\pm$ 3.8
Parkinson's Disease Sleep Scale (PDSS) total score	96.7 $\pm$ 24.8**	117 $\pm$ 19.2
Global Depression Scale (GDS-15) (no. (%) high risk)	55 (41.0)**	6 (6.5)
Berlin Questionnaire (no. (%) high risk for sleep apnea)	66 (49.3)**	32 (34.8)
STOP Questionnaire (no. (%) high risk for sleep apnea)	64 (47.8)	34 (37.0)
SF-36 (physical component score)	38.9 $\pm$ 9.4**	48.3 $\pm$ 10.7
SF-36 (mental component score)	46.7 $\pm$ 10.0**	53.1 $\pm$ 8.9

Parkinson's disease subjects vs. controls

*
 $p < .05$

**
 $p < .01$

Table 2

Characteristics of Parkinson's disease patients with high risk vs. low risk of sleep-disordered breathing on the Berlin Questionnaire

	Low risk (n=68)	High risk (n=66)
Age (years)	72.8±10.3	68.5±9.3**
Gender (no. male/no. female)	43/25	45/21
PD severity (no. mild (stage 1–2)/no. severe (stage 2.5–5))	29/39	18/47
Body mass index (kg/m ²)	24.4±4.2	29.3±5.6**
Mini-Mental Status Exam (MMSE)	27.7±2.6	27.6±3.0
Epworth Sleepiness Scale	8.0±4.4	11.8±5.9**
Parkinson's Disease Sleep Scale (PDSS) total score	100.8±21.5	92.5±27.4**
Global Depression Scale (GDS-15) (no. (%) high risk)	19 (27.9)	36 (54.5)**
SF-36 (physical component score)	41.1±8.5	36.7±9.8**
SF-36 (mental component score)	48.1±9.1	45.3±10.7

Parkinson's disease subjects vs. controls

**
p<.01