Comparison of Sleep Disturbance in Mild versus Severe Parkinson’s Disease

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INTRODUCTION

SLEEP DISTURBANCE IS A WELL-RECOGNIZED PHENOMENON IN PARKINSON’S DISEASE (PD). Sleep fragmentation with increased sleep latency, frequent prolonged awakening and decreased sleep efficiency have all been described. Furthermore, decreased rapid eye movement (REM) sleep and decreased slow wave sleep (SWS) have all been reported previously.1-6 Excessive daytime somnolence is also a prominent feature.7

The factors that disrupt sleep are multifactorial but the relative contribution of each is poorly understood. The severity of PD (perhaps via intrinsic CNS degeneration in sleep centers or due to associated motor phenomena) and drug effects (particularly L-dopa) are thought to be very important.1,2,4-6,8,9 Other factors include the aging process, depression, periodic leg movements (PLMs), vivid dreams and nightmares, hallucinations, painful leg cramps, inability to turn over in bed, nocturia, and REM sleep behaviour disorder.10-15

In clinical practice, it is the subgroup of patients with daytime sleepiness who are referred to sleep physicians. With this in mind, we endeavoured to study a subgroup of patients with subjective evidence of daytime sleepiness, to determine the relative importance of disease severity on their sleep.

METHODS

This study was approved by the Monash University Ethics Department and conformed to the Declaration of Helsinki guidelines. Informed consent was obtained from all patients prior to participation.

Patients

Patients were referred by their treating neurologists and recruited over a 6-month period. All had the clinical diagnosis of idiopathic PD. Disease severity was evaluated using the Hoehn and Yahr staging system as assessed by each patient’s neurologist. Daytime sleepiness was evaluated by the Epworth Sleepiness Scale (ESS) administered by the respiratory and sleep unit’s registrar. Patients with mild (Hoehn and Yahr 1 or 2) or severe (Hoehn and Yahr 4 or 5) disease and an Epworth score greater than 8 proceeded to the next phase of the trial. Patients with moderate disease (Hoehn and Yahr 3) or an Epworth score less than 8 were excluded. Patients proceeding to the next phase of the trial underwent overnight polysomnography and autonomic function testing and completed a series of questionnaires.

Epworth Sleepiness Scale

The ESS has been validated as a subjective measure of daytime sleepiness.16 The questionnaire asks patients to rate their chance of dozing off in 8 different situations and provides a score between 0 (least sleepy) and 24 (most sleepy). It is used exten-
sively in the assessment of patients with obstructive sleep apnea, but to our knowledge has never been applied to patients with PD. In normal subjects with a mean age of 36, the mean score is 5.9,16 Patients with mild sleep apnea have a mean score of 9.5. Considering that we were studying elderly patients, we used a cutoff score of greater than 8 to select a subgroup of sleepy patients.

**Hoehn and Yahr Staging**

The Hoehn and Yahr staging is a validated method of assessing the severity of PD.17 It takes into account the distribution of the patient’s disease and his/her level of disability. Scoring ranges from one (least severe) to five (most severe) (see appendix). We selected patients with scores of 1 or 2 versus 4 or 5 to ensure two distinct groups of mild and severe PD.

**Polysomnography**

We performed continuous nocturnal polysomnographic recording using a computerised system (“S-series” hardware with “W-series” software, Ver. 2.0 release 22, Compumedics Pty. Ltd, Melbourne, Aust.) with two electroencephalographic leads (C3-A2, C2-A1), submental electromyogram, electrocardiogram (lead 2), bilateral anterior tibialis surface movement sensors (piezoelectric), and a body-position sensor.

Respiration was monitored using a triple oronasal thermistor (Compumedics Pty, Ltd.). Respiratory effort was measured using thoracic and abdominal impedance plethysmography bands (Compumedics Pty. Ltd.). Continuous oxygen saturation was recorded with an oximeter (Datex-Ohmeda 3900 Louisville CO, USA).

Infrared video with sound was recorded. Staff also recorded the number of urinary voids overnight and any nocturnal vocalisations.

Sleep-stage scoring was according to the criteria of Rechtschaffen and Kales.18 This was performed manually by the same registered polysomnographic technologist who was blinded to the severity of the patient’s PD. Arousals and PLMs were also scored manually according to the American Sleep Disorders Association’s criteria.19 Apnea was defined as a decrease in airflow by greater than or equal to 80% associated with greater than or equal to 2% desaturation for at least 10seconds. Hypopnea was defined as a decrease in airflow by less than 80% associated with greater than or equal to 2% desaturation for at least 10 seconds.

| Patients enrolled in trial, with ratings of disease severity and somnolence. |
|---------------------------------|-----------------|-----------------|
| Mild PD  | Moderate PD  | Severe PD |
| HY=1,2  | HY=3          | HY=4,5        |
| ESS ≤ 8 | 17            | 5              | 9              |
| ESS > 8 | 16*           | 5              | 11†            |

PD=Parkinson’s disease; HY=Hoehn and Yahr stage; ESS =Epworth sleepiness scale.

* 11 of these patients proceeded to next phase of trial.

† 7 of these patients proceeded to next phase of trial.

**Questionnaires**

The Beck Depression Inventory is a self-reporting questionnaire made up of 21 items, which assess for the presence and severity of depression symptoms. A score ranging from 0 (no symptoms) to 63 (all symptoms) is obtained. It has been validated as a screening test for depression in a number of chronic illnesses (e.g., diabetes), with a sensitivity and specificity of 70%, using a cut-off score of 16 or greater.20

The Nottingham Health Profile (NHP) is a quality-of-life questionnaire. It provides a profile of perceived health problems in the areas of energy, pain, emotional reactions, sleep, social isolation, and physical mobility. A score ranging from 0 (least affected) to 100 (most affected) is obtained for each category. It can be used to compare patients with chronic disease. There are accepted values in each category for both fit elderly patients and those with chronic illness.21

We constructed a questionnaire that asked patients to estimate the number of times per night they were aware of nocturnal rigidity, painful leg cramps, nightmares, and hallucinations. A medication list, including dosages, was obtained from all patients.

**Autonomic Function Testing**

Autonomic function was assessed using cardiovascular reflexes. Previous studies have demonstrated that parasympathetic testing better reflects clinical evidence of autonomic dysfunction in patients with PD.22 Heart-rate responses to (a) Valsalva manoeuvre (b) deep breathing, (c) standing, were used to test for parasympathetic dysfunction. Patients were classified as having autonomic dysfunction if at least two of the three tests were abnormal. An abnormal Valsalva ratio was defined as less than 1.10; an abnormal heart rate response to deep breathing was defined as less than 10 beats per minute; an abnormal heart-rate response to standing (RR ratio 30:15) was defined as greater than 1.0.22,23

**Data Analysis**

We needed 16 patients (8 in each group) to detect a difference of 20-arousals per hour between the two groups, with a power of 0.8.

Data were examined from the overnight polysomnography, questionnaires, and autonomic-function testing. The mild disease group was compared to the severe group. The paired t-test was used to compare normally distributed, and the Mann-Whitney-U test for nonparametric data. All analyses assumed a type-1 error rate of 5%.

Regression analysis was performed using combined data from the two groups, to determine if any of the primary outcome variables was independently related to any of the covariates.

**RESULTS**

A total of 63 patients were enrolled. Of these, 33 were classified with mild, 10 with moderate and 20 with severe PD. On the ESS 31 patients had a score less than or equal to 8 and 32 had a score of greater than 8 (see Table 1). From this sample, 27 patients were eligible to proceed to the next stage of the study (met Hoehn and Yahr and Epworth staging criteria). Of these, 9 patients refused to participate further, most citing the inconve-
nience of a sleep study as the major reason. This left a total of 18 patients, 11 with mild and 7 with severe disease, to proceed to polysomnography, questionnaires, and autonomic function testing.

**Group Characteristics**

There was no significant difference in age, sex or ESS between the two groups. The mean dose of L-dopa was higher in the severe disease group but this did not reach statistical significance. Two patients from each group were on an additional dopamine agonist. As expected, there was a significant difference in Hoehn and Yahr staging between the two groups, given this was used as the selection criterion for each group (see Table 2).

**Polysomnography**

Both groups had sleep fragmentation with increased sleep latency, frequent arousal, and poor sleep efficiency. There was also a paucity of REM sleep. The frequency of PLM overnight was also increased. However, there were no significant differences in any of these parameters between the two groups.

The only significant difference was the higher number of voids overnight in the severe group.

The apnea/hypopnea index was within normal limits in both groups, and there was no significant difference between the two groups (see Table 3).

**Questionnaires**

The BDI scores were high in both mild and severe disease groups. Using a cutoff score of 16, there was evidence of depression in 5 of 11 (45%) mild patients and 3 of 7 (43%) severe patients. However, there was no statistically significant difference between the two groups (see Table 4).

Nocturnal rigidity, painful leg cramps, vivid dreams and hallucinations were infrequent in both groups, and there was no difference between the two groups.

**Autonomic Function Testing**

Among the mild patients 4 of 11 (36%) had autonomic dysfunction, compared with 5 of 7 (71%) of the severe patients. Although this represents a high incidence of autonomic dysfunction relative to the normal population, there was no significant difference between the two groups (see Table 4).

**Regression Analysis**

Regression analysis showed an independent relation between normal autonomic function and increased sleep efficiency (p-value 0.03). There was also an independent relation between a decrease in L-dopa dose and an increase in REM sleep (p-value 0.02).
was found to be prevalent, particularly in the severe disease group.

The reduction in sleep efficiency in PD patients has been reported previously.1,2,5,6 It has been suggested that disease severity is the most important factor. Interestingly, our study found the mild-disease group to have an equally poor sleep efficiency. This points to a greater role for other factors, such as drug effects, in causing sleep disturbance in this subgroup of PD patients with subjective daytime somnolence. Chronic L-dopa usage in PD may contribute to daytime somnolence, initiation and maintenance insomnia, altered dreams, nocturnal vocalization, hallucinations, and decreased REM sleep. The mechanism is poorly understood but could involve central dopaminergic or serotonergic effects.8,9 Our regression analysis supported this notion by showing a relation between lower L-dopa dose and higher levels of REM sleep.

Other factors include frequent PLMs associated with arousals. This was recently described even in drug naïve patients with PD.14 Nocturia appears to be an important contributor, particularly in the severe disease group. Detrusor hyperreflexia is a recognized cause of bladder dysfunction in PD. This may relate to the disease itself, to L-dopa use, or to loss of L-dopa efficacy at night.24 Additional causes of nocturia include dysfunction of the striated urethral sphincter and pelvic floor muscles, autonomic neuropathy and obstruction due to anticholinergic medications.25 Autonomic dysfunction may contribute to sleep disturbance independently, or as a result of nocturia. Our regression analysis suggested patients with normal autonomic function had higher sleep efficiency.

It has been postulated that sleep disturbance tends to correlate with disease severity in PD.4 This implies that (a) neuronal degeneration in motor areas and sleep centers progress simultaneously or (b) motor phenomena (e.g., tremor, PLMs, myoclonus) that parallel disease progression play a major role in producing sleep disturbance. However, we contend that measures of motor functional severity, such as the Hoehn and Yahr staging, may be an inaccurate predictor of sleep abnormality. If neuronal degeneration in sleep centers is dissociated from motor areas, then sleep disruption will not necessarily reflect motor impairment. A better predictor of sleep disruption may be an assessment of subjective daytime sleepiness such as the ESS. As an example, cerebral degeneration that produces dementia in PD may not necessarily parallel the motor impairment.26 The mini mental state questionnaire or even neuropsychiatric testing is used to screen for dementia. Further research to test this hypothesis would be required.

In this study, the small sample size and multiple factor analysis could have introduced type-2 errors. The multifactorial nature of the sleep disturbance means larger trials are needed to validate these results. Another limitation was with first-night effect, as only single night polysomnography was performed. Finally, questionnaires are user dependent and under-reporting can occur in cognitively impaired patients. This could have biased patient selection with regards to the ESS. Furthermore, we acknowledge the controversy in using the Epworth scale as a surrogate marker of excessive daytime sleepiness. While it may correlate with a patient’s subjective assessment of their sleepiness, a poor correlation with objective measures, such as the multiple sleep latency test,27,28 has been reported.

In summary, we found that in a subgroup of patients with idio-pathic PD and excessive daytime somnolence, their motor and functional severity did not predict their level of sleep disturbance. We postulate that questionnaires assessing daytime somnolence are more reliable.

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REFERENCES


APPENDIX

Hoehn and Yahr staging

1=unilateral disease; 2=bilateral disease; 3=mild to moderate bilateral disease, postural instability; 4=severe disability; 5=wheelchair bound or bedridden unless aided.