Comparison of the Sleep Disorders in Familial Vs Sporadic Parkinson's Disease – a Prospective Study.

Thesis submitted in fulfilment of the rules and regulations for DM Degree Examination of Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram

By

Dr. Anis Jukkarwala

Resident in Neurology

Month and Year of Submission: October 2011

CERTIFICATE

I, Dr. Anis Jukkarwala hereby declare that I have actually carried out the project under report.

Place: Thiruvananthapuram **Signature:**

Date: 07-10-2011 **Dr. Anis Jukkarwala**
Resident in Neurology

Forwarded. He has carried out the project under report.

Signature: **Signature:**

Dr. Syam K. Nair (Thesis Guide)
Assistant Professor
Department of Neurology,
SCTIMST

Prof. (Dr.) M. D. Nair
Professor & Head,
Department of Neurology,
SCTIMST.

Acknowledgement

I take this opportunity to sincerely thank Prof. K. Radhakrishnan, Director, SCTIMST, for providing me the opportunity to do this study.

I am indebted to Prof. M. D. Nair, Senior Professor and Head, Department of Neurology for the constant support and encouragement during the period of this study.

I sincerely thank Dr. Syam K. Nair, Dr. Asha Kishore, Dr. Ashalatha Radhakrishnan, who were my guide for the study, for their expert guidance, review, kind help, and keen interest at each and every step during the completion of this study.

I sincerely thank Mr Gangadhara Sarma, Psychologist, for helping patients in filling sleep questionnaires & Mr. Unnikrishnan, Medico social worker, for arranging appointment of patients for polysomnography.

I sincerely thank Prof Sankara Sarma for carrying out the statistical analysis.

I express my gratitude towards all the patients who took part in this study.

Dr. Anis Jukkarwala

Contents

INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by resting tremor, rigidity, bradykinesia & postural instability with good response to L-dopa & neuropathology characterized by degeneration of dopaminergic neurons in the substantia nigra pars compacta coupled with intracytoplasmic proteinaceous inclusions known as Lewy bodies (1,2).

The precise etiology of PD is unknown and the relative contributions of genetic and environmental factors may vary in different cases (3). Those without a positive family history & classic late age of onset are sporadic forms whereas those patients with a positive family history & early age of onset (usually less than 40 years) are classified as familial PD.

Approximately 10–15% of patients with the typical clinical picture of PD have a positive family history compatible with a mendelian (autosomal dominant or autosomal recessive) inheritance (4).

Mutations within the genes at 6 loci (α-synuclein, LRRK2, Parkin, DJ1, PINK1 and ATP13A2) have conclusively been demonstrated to cause familial parkinsonism (5,6,7,8,9,10). α-synuclein & LRRK2 are implicated in autosomal dominant PD while Parkin, DJ1, PINK1 and ATP13A2 are autosomal recessive forms. These genes are found in selective ethnic populations and a few of them have atypical clinical features like myoclonus and hypoventilation in α-synuclein (5), dementia with lewy bodies in E46K substitiution of α-synuclein gene (11) & progressive supranuclear gaze palsy like presentation in ATP13A2 related parkinsonism (10).

Madegowda et al., reported Parkin gene mutations in 2 out of 20 cases of familial early onset PD from South India (12). Punia et al., did LRRK2 mutation testing in 1012 Indian PD patients and found a heterozygous G2019S mutation in a single young PD patient (13). Another recent study from South India testing for LRRK2 G2019S mutation in 86 familial PD cases did not find even a single case positive for the mutation. These studies suggest that the frequency of genetic mutations in PD shows significant variation based on ethnicity (14).

It is well known that PD is also associated with many nonmotor features including various types of sleep dysfunction. A community based study found that nearly two thirds (60-70%) of the patients with Sporadic PD had sleep disorders, significantly more than among patients with diabetes (46%) and healthy control subjects (33%) (15).

Patients with PD can have excessive daytime somnolence (EDS) as well as nocturnal sleep problems (16). The etiology of sleepiness in PD patients is multifactorial; dopaminergic medications as well as disease related factors like duration and severity are associated with EDS in PD (17,18,19,20,21). Nocturnal sleep disturbances may be grouped into four broad categories; insomnia, secondary to motor dysfunction, urinary and neuropsychiatry problems (22). Patients with PD have significantly less total sleep time and reduced sleep efficiency (23). Sleep fragmentation and early awakening are seen more frequently than age matched controls (16). The motor function related sleep disturbances include nocturnal akinesia, restless leg syndrome and periodic limb movements during sleep; the neuropsychiatry problems include rapid eye movement (REM) behavior disorder, hallucinations, nocturnal vocalizations & nightmares (24).

The sleep disturbance correlates with disease severity & duration, Schwab and England Score, Unified Parkinson Disease Rating Scale (UPDRS) motor score & levodopa dose (25).

Braak proposed a staging model for the progression of pathological process in PD which starts in the brainstem & progresses in a topographically predictable sequence upto neocortex in last stage (26). During stages 1-2, the inclusion body pathology remains confined to medulla, pontine tegmentum & anterior olfactory nucleus. Due to the presence of sleep centres in brainstem, sleep related problems often predate classic motor manifestations of PD. There are no such studies of pathology in Familial PD.

Based on these differences, it would be of interest to see whether the pattern of sleep dysfunction is different in two forms of PD – familial & sporadic, which would indicate different pattern of involvement of brainstem centres.

There have been various studies on sleep disorders in sporadic PD. However, sleep disorders have never been systematically evaluated in familial forms of PD. Moreover, there have been no study so far comparing pattern & prevalence of sleep disturbances in sporadic & familial PD.

REVIEW OF LITERATURE

Etiological subtypes of PD

Parkinson's disease is unlikely to be a single disease entity; it represents a diversity of conditions resulting in a common clinical presentation (3). The precise etiology of PD is unknown, and the relative contributions of genetic and environmental factors are widely debated. A positive family history has been recognized as a major risk factor for PD (27) and may point to a genetic etiology.

Genetic susceptibility plays a stronger role in younger onset cases, whereas environmental factors play a stronger role for older onset cases (28,29). Thus, young onset cases and cases with a positive family history are likely to have a predominantly genetic basis while cases with older age of onset have a stronger etiological contribution from environmental factors (30, 31).

Sleep disorders in Sporadic PD

Nearly 98% of patients with Parkinson's disease (PD) may suffer at some time from nocturnal symptoms that can disturb their sleep (32). A community-based study reported 60% of patients with PD with sleep problems, compared with 33% of healthy controls with the same age and sex distribution (33). Another community based study found that nearly two thirds of the patients with PD had sleep disorders, significantly more than among patients with diabetes (46%) and healthy control subjects (33%) (15). Oerlemans et al, using a sleep questionnaire mailed to around 400 PD patients, found a high prevalence of abnormalities including restless leg syndrome (RLS) and REM sleep behavior disorder (RBD) (34). In spite of this high prevalence

neurologists fail to recognize the sleep disturbances in Parkinson's disease patients in nearly half of the routine office visits (35). This stresses the need to develop disease specific questionnaires, validate them in the regional population and popularize them among neurologists taking care of patients, for more efficacious identification of sleep related problems in PD and better management.

There have been a number of questionnaire / interview based studies on sleep disturbances in patients with Parkinson's disease (17, 18, 19, 20, 21, 25). But majority of them focused on excessive day-time somnolence (EDS). The EDS of PD is probably multifactorial and needs a comprehensive assessment (21). The Parkinson's Disease Sleep Scale (PDSS) has been developed for the comprehensive assessment of sleep and nocturnal disability in PD (36) and is disease-specific. The PDSS scores in PD and control groups differ significantly. Individual items of the scale showed good discriminatory power between PD and controls. Overall tendencies were the same across different ethnic groups (37). This scale has been validated in non-English patient populations including Chinese (38), Brazilian (39), Japanese (40) and Spanish (41).

Ferini-Strambi did sleep studies in a specific subgroup of patients with PD- i.e, 26 untreated patients with early PD and found that sleep architecture and respiration did not differ significantly from age matched controls, though there was evidence of defective cardiac autonomic control during sleep (42). Diederich et al (43) found that the sleep destructuring in PD is related to disease duration; however the study was retrospective and only patients with obvious sleep related complaints came for the study. Dhawan et al (44) studied the nature of sleep dysfunction in Parkinson's disease using the Parkinson's disease sleep scale and selective

Polysomnography. They concluded that nocturia, nighttime cramps, dystonia, tremor and daytime somnolence are important nocturnal disabilities in PD patients compared to age matched healthy controls. Arnulf et al (45) did PSG in patients who had complaints of EDS & found that EDS was not dependent on nocturnal sleep abnormalities, motor and cognitive impairment, or antiparkinsonian treatment. Hogl et al (46) assessed the effect of sleep benefit on motor performance in Parkinson's disease (PD) and analyzed its relation to pharmacologic and sleep measures by polysomnographic studies . They found that patients with sleep benefit had more severe interdose "off" than those without. Levodopa concentrations and polysomnographic findings were similar in both conditions. Roth et al (47) performed a polysomnographic study along with multiple sleep latency test (MSLT) in 24 patients of PD on dopamine agonists; 16 complaining of unintended sleep episodes (SEs) & 8 without. They found that there was no difference between the two groups with respect to nocturnal PSG measures, ESS scores & MSLT findings. They concluded that SEs in PD patients occur upon a background of excessive daytime sleepiness and are unrelated to nocturnal sleep or use of a specific DA. Maria et al (48) performed PSG in 15 patients with PD to investigate the presence of sleep breathing disorders and found that sleep breathing disorders, predominantly obstructive, were common in PD and those events correlated with the severity of the disease. Gagnon et al (49) examined 33 consecutive patients with PD with clinical history and Polysomnography, aimed to find out the prevalence of RBD. They found out that nearly one-third had RBD, proven by PSG and half of these would have been missed by clinical history alone. Wetter et al did a PSG study in 10 patients with PD , 10 patients with MSA and age and sex matched controls and concluded that sleep disruption and increased motor activity during REM and NREM sleep are a frequent finding in PD and MSA (23). Eisensehr et al (50) retrospectively reviewed the PSG data in 19

patients with PD and 273 patients with other sleep disorders and found that RBD was prevalent in 47% of PD patients compared to 1.8% of non-PD patients. The sensitivity and specificity for a clinical interview in diagnosing RBD was nearly 100% in non-PD patients, while the sensitivity was poor (33%) for patients with PD. The authors concluded that PSG is indicated for the diagnosis of RBD in PD. Wetter et al (2001) (51) prospectively did a polysomnographic study of 45 patients with PD and found that 40% had REM sleep abnormalities and there was a positive correlation with disease duration. The study by Diederich et al (2005) (52) was a retrospective one, aimed at investigating the impact of nocturnal respiration on sleep continuity and architecture in PD. Young et al (53) compared the objective sleep parameters obtained by Polysomnography, from patients with early PD and advanced PD. There was no significant difference between the two groups and both groups fared poorly compared to historical normal controls.

There have been only few studies examining the sleep disturbances in unselected PD patients with PDSS and examining the correlation with PSG abnormalities. Uemura et al (40) examined sleep disturbance in patients with Parkinson's disease (PD) using PDSS, Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS), and polysomnography (PSG) in Japanese PD patients. PSG was performed on 33 of 79 PD patients and the correlation between the PDSS and PSG was also examined. PDSS total scores and subscales from patients with PD were significantly lower than those in controls. The total PDSS score also correlated with sleep efficiency as measured by PSG. The authors concluded that PDSS appeared to be a reliable tool to evaluate the characteristics of sleep disturbances in Japanese PD patients. Norlinah et al (54) performed a cross-sectional study involving 46 Malaysians with PD using PSG and standardized translated Parkinson’s disease sleep scale. They concluded that the prevalence of sleep disorders

based on PSG and PDSS in Malaysian PD patients was high, the commonest being sleep fragmentation and SDB, while EDS was the least prevalent. Problem specific subitems of the PDSS were more accurate in predicting the relevant PSG-related changes compared to the PDSS as a whole.

Pathogenesis of sleep disorders in PD

The pathophysiology of sleep disturbance in PD is complex and multifactorial. The degeneration of central sleep regulation centres in the brainstem and thalamocortical pathways is implicated. Sleep disturbance may precede motor symptoms (55), and this probably reflects the degeneration of areas, such as the raphe nucleus (serotonin) and locus coerulus (noradrenaline), which constitute those pre-clinical stages 1 and 2 of the pathological staging of PD proposed by Braak [26]. These nuclei appear to play a critical role in thalamocortical arousal and the sleep–wake cycle, and their degeneration leads to the disruption of basic REM and non-REM sleep architecture, manifesting as insomnia, parasomnias and hallucinations [56, 57]. The pedunculopontine nucleus and the retro-rubral nucleus have strong influences on REM atonia and phasic generator circuitry and have been implicated in the pathogenesis of RBD [57]. A flip-flop-switch pattern of regulation of sleep– wake cycle has been proposed by Saper [58], suggesting that the brain can be either ‘off ’ (asleep by activating the ventrolateral preoptic area, the sleep promoter) or ‘on’ (in quiet wakefulness with the activation of the tuberomamillary nucleus, the wake-promoting area along with locus coerulus and the raphe nuclei). The internal rhythm between the two switches is regulated by the suprachiasmatic nucleus. Hypocretin 1 (orexin), a hypothalamic peptide, virtually undetectable in narcolepsy, is now thought to have a complex relationship with the dopaminergic systems in the basal ganglia and may function as an

external regulator of the flip-flop switch promoting wakefulness [57, 59]. In PD, dopaminergic dysfunction and neuronal degeneration can destabilise this switch and its regulators, promoting rapid transitions to sleep intruding on wakefulness. However, speculation that dopaminergic medications produce sleepiness by reducing levels of the hypothalamic neuropeptide hypocretin 1, insufficiency of which is implicated in narcolepsy, was not confirmed by studies of cerebrospinal fluid in three patients with PD and excessive day-time sleepiness associated with dopamine agonist use [60].

Familial forms of PD

Approximately 10–15% of patients with the typical clinical picture of PD have a positive family history compatible with a mendelian (autosomal dominant or autosomal recessive) inheritance (4). As a rule, age at onset in many (but not all) of these patients is younger than that of patients with sporadic disease, but no other specific clinical signs or symptoms distinguish familial from sporadic cases.

Genes Causing Autosomal Dominant Forms of Parkinsonism

To date, at least two genes, α-*synuclein* (α -*SYN*), and recently, leucine-rich repeat kinase 2 (*LRRK2*) are known to cause autosomal dominant PD.

PARK1/4: α -*SYN*

The first "PD gene" was mapped to the long arm of chromosome 4 in a large family with dominant inheritance and Lewy body pathology, and identified as the gene for α -*SYN* (21). Over the years, only three different point mutations have been recognized (5, 61, 62) each representing

a single mutational event, all in large, multigenerational families. α -*SYN* point mutations have not been found in sporadic PD (63).

The currently favored hypothesis states that the amino acid changes in the α -*SYN* protein associated with PD may lead to an increased tendency to form aggregates (64), although the precise relationship between aggregation and cellular dysfunction and cell death is unknown. A direct link between α -*SYN* and PD is supported by the recent discovery that not only point mutations, but also multiplications of the wildtype sequence of the α -*SYN* gene (duplications and triplications) cause autosomal- dominant parkinsonism with or without dementia with α-*SYN* inclusions (65, 66).

The clinical picture in the affected subjects from pedigrees with α -*SYN* mutations or multiplications ranges from typical idiopathic PD to dementia with Lewy-bodies (62), although age at onset is lower (mean of about 35–45 years with a wide range) and progression appears to be more rapid than in sporadic cases (67, 68).

PARK8: Leucine Rich Repeat Kinase 2 (LRRK2)

Another locus for a dominant form of PD has been mapped in a large Japanese family to the pericentromeric region of chromosome 12 and named PARK8 (69). The disease is caused by point mutations in the gene for *LRRK2* (70, 71) & the encoded protein has been called "dardarin"(71).

LRRK2-associated PD is remarkable for several reasons. First, mutations in the *LRRK2* gene appear to be the most common cause of autosomal-dominantly inherited parkinsonism discovered so far (72). Second, clinical signs and symptoms resemble typical sporadic PD in

most families. This is true also for age of onset, which is on average in the late fifties and sixties in the families described so far.

Current experimental evidence suggests that dardarin mutations may be associated with an increased kinase activity.

Autosomal Recessive Forms of Parkinsonism

So far, three mutations have been identified: *parkin* (*PARK2*), *PINK1* (*PARK6*), and *DJ-1* (*PARK7*).

PARK2: Parkin

The first genetic locus for autosomal- recessive juvenile parkinsonism was mapped to a large gene called *Parkin* on chromosome 6 (6). Clinically, these patients suffer from early onset L-dopa-responsive parkinsonism and often develop early and severe L-dopa-induced motor fluctuations and dyskinesias. Some show diurnal fluctuations, with symptoms becoming worse later in the day. Dystonia at onset of the disease is common.

Parkin is a protein found in the cytosol but also associated with membranes, functions in the cellular ubiquitination/protein degradation pathway as a ubiquitin ligase (73). It has been hypothesized that the loss of *parkin* function may lead to the accumulation of a nonubiquitinated substrate that is deleterious to the dopaminergic cell but, due to its nonubiquitinated nature, does not accumulate in typical Lewy bodies.

PARK6: PINK1

Mutations in the *PINK1*-gene (PARK6) have been identified as another cause for autosomal-recessive early-onset parkinsonism (8). This gene is particularly interesting within the context of

the findings linking PD to mitochondrial dysfunction and oxidative stress, as *PINK1* encodes a mitochondrially located protein. Mutations in the *PINK1*-gene are much less common than *parkin* mutations (74-77).

PARK7: DJ-1

Mutations in the *DJ-1* gene (PARK7) are another rare cause of autosomal-recessive parkinsonism (7, 78, 79). The clinical picture with early-onset and slow progression is similar to the other recessive Parkinson syndromes. The normal function of *DJ-1* and its role in dopamine cell degeneration is unknown, but there is evidence that links *DJ-1* to oxidative stress response and mitochondrial function.

OTHER GENES AND LOCI

Several other loci have been mapped in families with PD, but either the genes have not yet been identified, or their role is still somewhat controversial.

A missense mutation in the gene for ubiquitin carboxy- terminal hydrolase L1 gene (*UCHL1*, *PARK5*), which is located on chromosome 4p has been identified in affecteds in a single family of German ancestry (80). To date, no other bona fide pathogenic mutations of this gene have been identified.

A dominant locus has been described on chromosome 2p13 (PARK3) (81). Clinical features relatively closely resemble those of sporadic PD. So far, however, the gene has not been identified.

The discovery of above mentioned genes & their mutations have highlighted the contribution of genetics in PD. Some mutations like Parkin have clearly been shown to be more common in early onset PD & familial cases (82). There are very few studies of similar mutations in Indian population (12,13,14).

Sleep disorders in Familial PD

There are no studies of sleep disturbance in Familial PD. However, few case reports are available.

Tuin et al., performed sleep interviews & PSG study in a Spanish family with PINK1 mutations (PARK6) (83). They found that all siblings had good subjective and objective sleep quality. Restless legs syndrome and rapid eye movement (REM) sleep behaviour disorder (RBD) were not observed. They postulated that good sleep quality and the absence of RBD might be a useful diagnostic guide in the differential diagnosis of sporadic PD versus PARK6.

Juan et al., (84) performed PSG studies in 4 of the 7 patients and in 2 asymptomatic carriers of a novel mutation in the α-synuclein gene (E46K) presenting with parkinsonism & dementia. A severe loss of both REM and non-REM sleep was observed in 3 patients and mild sleep dysfunction in carriers. Though 2 patients complained of bizarre behavior at night, RBD could not be recorded in any case. They concluded that sleep disorders were common in synucleinopathies.

AIMS & OBJECTIVES

To compare the prevalence and pattern of sleep disturbances in Familial PD & Sporadic cases of PD with negative family history.

MATERIAL & METHODS

Study design, inclusion and exclusion criteria:-

Inclusion criteria for the Familial PD group:

1. Diagnosis of PD by UKPD Brain bank diagnostic criteria (85) for Parkinson's disease.
2. One or more of the family members with a documented diagnosis of PD.
3. No comorbid illness/condition likely to cause sleep dysfunction (like substance abuse, obstructive airway disease, cardiac failure).

Inclusion criteria for sporadic PD patients

1. Diagnosis of PD by UKPD Brain bank diagnostic criteria (85) for Parkinson's disease.
2. Matched with familial PD patients for duration of the disease and Hoehn & Yahr stage.
3. No family member with a documented diagnosis of PD (other than proband) in preceeding three generations or any successive generation.
4. No comorbid illness/condition likely to cause sleep dysfunction (like substance abuse, obstructive airway disease, cardiac failure).

The patients were recruited from **Movement Disorders clinic of *SCTIMST, Thiruvananthapuram, Kerala*** were recruited. Written informed consent was obtained from all patients prior to enrolment. The study was approved by the institution's Technical Advisory Committee and the Ethics Committee. Institute's funding was available for the project.

Clinical assessments:-

Familial & sporadic PD patients who participated in the study were interviewed using the structured proforma during their routine clinic visits. All patients underwent a detailed clinical examination and the following parameters were recorded :

- **age of onset (in yrs)**
- **duration of motor symptom (in yrs)**
- **clinical subtype of PD (tremor vs bradykinesia dominant vs mixed)**
- **Hoehn & Yahr (H & Y) stage**
- **comorbid illness (diabetes, HTN, others)**
- **L-dopa equivalent dose, individual PD medications with doses**
- **other medications**

Questionnaires:-

Symptoms indicating sleep dysfunction were collected using Standardised questionnaires - **Parkinson's Disease Sleep Scale (PDSS)** (36) **& Epworth Sleepiness Scale (ESS)** (86).

PDSS is a visual analogue scoring method, addressing 15 commonly reported symptoms associated with sleep disturbances in PD, with good test- retest reliability (36). A higher PDSS score reflects better sleep quality. The patients completed the PDSS based on their experience in the past week. We used a standardized translated version in Malayalam language for patients who were unable to perform the test in English. The translation was done by a bilingual clinical psychologist who is well versed with similar tasks. Patients were asked to fill in the PDSS in the consultation room; involvement of the caregiver was also encouraged. The severity of symptoms were reported by marking a cross along a 10 cm line (labelled from worst to best state).

Responses were quantified by measuring the distance along each line to the intersection with the cross in centimetres, to the nearest 0.1 cm. Thus scores for each item range from 0 (symptom severe and always experienced) to 10 (symptom-free). The maximum cumulative score for the PDSS is 150 (patient is free of all symptoms). The items of the PDSS address the following:

- **overall quality of night's sleep (item 1);**
- **sleep onset and maintenance insomnia (items 2 and 3);**
- **nocturnal restlessness (items 4 and 5);**
- **nocturnal psychosis (items 6 and 7)**
- **nocturia (items 8 and 9);**
- **nocturnal motor symptoms (items 10–13);**
- **sleep refreshment (item 14);**
- **daytime dozing (item 15).**

In addition to PDSS, **ESS** was filled in all patients. ESS consists of 8 items intended to measure daytime sleepiness (86).

Polysomnography (PSG):-

All patients underwent an 8-h standardized overnight PSG using Biological Sleep Scan machine in the Sleep Disorders Centre & results were evaluated with the help of a Qualified Sleep Specialist.

PSG technique:

Patient instructions:

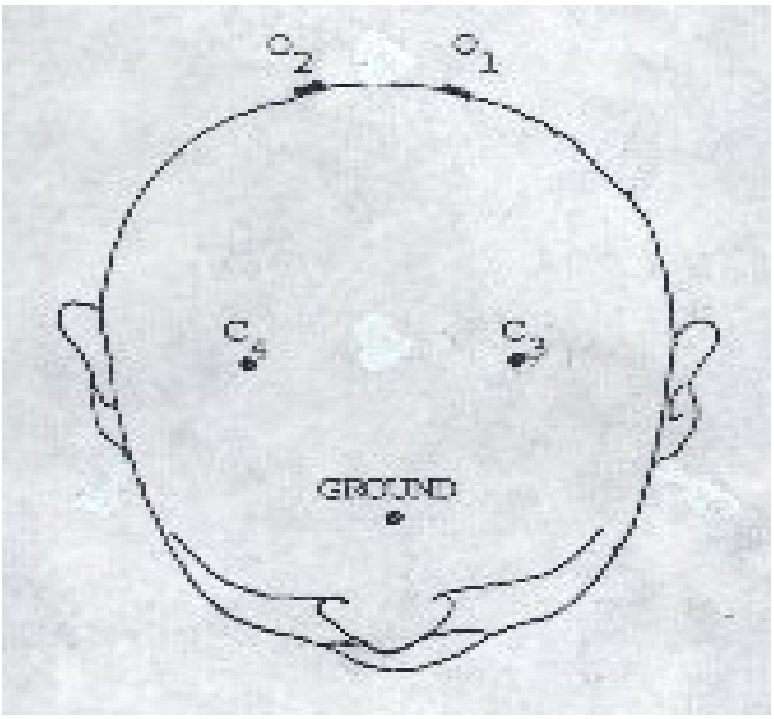
All patients were instructed to reach sleep lab at least 90-120 min before their usual sleep time in night. Before coming to the study the patients were advised to prepare a sleep diary of preceeding 2 weeks. Patient were instructed to drink less water & not to take tea or coffee after 4' O clock on the day of scheduled PSG. Also they were told to keep their hair clean.

Preparations:

The study was started with biological calibration (like eyes open, eyes closed, blink 5 times, mimic snoring, hold breath for 10 seconds, move the right and left leg, grind teeth, etc.). Same was done at the study end.

Technique:

1. EEG recording:-
    - Non polarisable Ag-AgCl electrodes were attached with a conducting paste.
    - Limited EEG montage including bilateral central, occipital and ear electrodes was used.
    - Filter settings HFF 70 Hz and LFF 0.3 Hz
    - Sensitivity 5-10 micro volt/mm
    - Paper speed 30 sec/ page.



2. Electrooculogram:-

    - Ag-AgCl cup electrodes were used.
    - One electrode was placed 1cm lateral and superior to the outer canthus, another inferior to the outer canthus on the opposite side.
    - Sensitivity and filter settings same as that of EEG recording.

3. Chin EMG:-

    - Regular surface EMG electrodes were placed, one on the tip of the jaw and 2nd 3 cm posterior and lateral.
    - Sensitivity 2 µvolt/mm, LFF 5 & HFF 70 Hz.

4. Tibialis anterior (TA) EMG:-

    - An electrode was placed over TA muscle.

- Sensitivity and filter settings same as that of chin EMG.

5. Nasal & oral airflow:-
    - Were measured using thermistors, fitted in or near the nostrils.

6. Thorax & abdominal movements:-
    - Piezoelectric belts were tied around chest & abdomen.

7. Oxygen saturation:-
    - Pulse oximeter was placed over finger tip.

8. Electrocardiogram:-
    - Two EKG electrodes were placed under the clavicle on each side of the chest.
    - Filter settings were kept at LFF 1 Hz and HFF 70 Hz with sensitivity of 50µ volt/mm.

9. A snore electrode was placed near trachea.

10. A body position sensor was placed over the abdominal or thoracic belt.

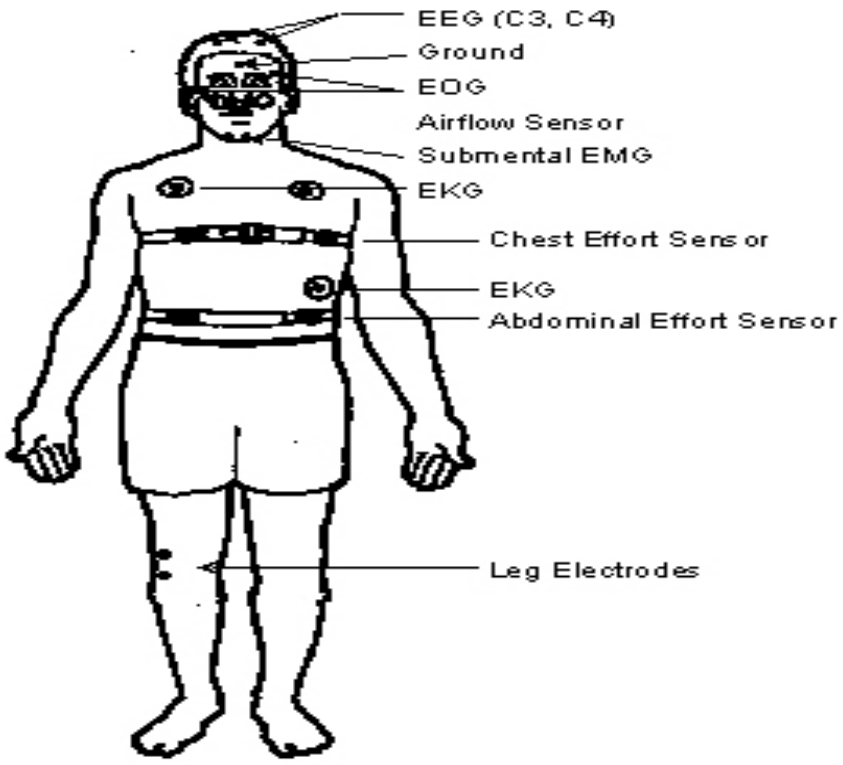


Table No. 1. Summary of recording montages:

Channel	Sensitivity (in µvolt/mm)	Filters, LFF/HFF (Hz)
C4-A1	7	0.3/70
O1-A2	7	0.3/70
C3-A2	7	0.3/70
O2-A1	7	0.3/70
L EOG	7	0.3/70
R EOG	7	0.3/70
Chin EMG	2	5/100
EKG	50	5/70
L TA EMG	3-7	5/70
R TA EMG	3-7	5/70

Nasal thermistor	-	0.1/15
Oral thermistor	-	0.1/15
Thoracic movt	-	0.1/15
Abdominal movt	-	0.1/15
Snore	-	5/70

The following PSG parameters were obtained:

Total sleep time (TST)

Sleep latency (duration to sleep onset)

Sleep efficiency (percentage of total sleep duration over total time in bed)

Duration of Stage 1, 2, slow wave & REM sleep

Apnea–hypopnea index (AHI)

Arousal index (AI)

Periodic limb movement index (PLMI)

Criteria used to score PSG parameters (87, 88):

Arousal was scored if there was any shift in EEG frequency (including alpha, beta, theta) lasting for 3-10 seconds. In REM sleep arousal was scored only when accompanied by a concurrent increase in submental EMG amplitude.

Arousal index was defined as number of arousals per hour of sleep.

Sleep fragmentation was defined as frequent microarousals lasting >3 s and <10 s with AI of ≥ 10/h.

Apnea was scored when there was ≥ 90% reduction of airflow with or without oxygen desaturation.

Hypopnea was scored when there was ≥ 50% reduction of airflow accompanied by ≥ 3% oxygen desaturation.

Apnea–hypopnea index (AHI) was defined as number of apneas and hypopneas per hour of sleep.

Sleep disordered breathing (SDB) was defined as the presence of 5 or more apneic or hypopneic events per hour (AHI) & graded as Mild: 5.0–15; Moderate: 15.1–30 & Severe: >30.

Periodic limb movements (PLM) was scored when minimum 4 consecutive limb movements of duration 0.5-10 seconds, amplitude 8 μV & periodicity 5-90 seconds were seen.

Periodic limb movement index (PLMI) was defined as the number of PLM occurring per hour of sleep and graded as Mild: 5–15; Moderate: 15.1–30 & Severe: >30.

STATISTICAL ANALYSIS

- **For categorical variables, percentages were compared by Fisher's exact test.**
- **For quantitative variables, Mann-Whitney test was used.**
- **p value ≤ 0.05 was considered significant.**

SPSS version 17 was used for data analysis. Statistical analysis was done with the help of a medical statistics expert.

RESULTS

The study included **20 cases of Familial & 20 cases of Sporadic PD.**

Demographic & clinical features:

In the Familial PD group, 12 (60%) patients had single affected family member, 7 (35%) patients had 2 affected family members & 1 (5%) patient had 3 affected family members (other than proband). This is shown in Table 1.

Table No.1. No. of family members affected in Familial PD patients (excluding the proband).

No. of family members affected	No.of patients (%)
1	**12 (60)**
2	**7 (35)**
3	**1 (5)**

Majority of patients in both groups had tremor dominant PD. Table 2 shows the classification of patients in both groups depending on clinical subtype.

Table No. 2. Classification of patients based on predominant clinical manifestation.

Subtype	**Familial PD;** **n (%)**	**Sporadic PD;** **n (%)**
Tremor dominant	**17 (85)**	**17 (85)**
Rigid-bradykinetic	**2 (10)**	**2 (10)**
Mixed	**1 (5)**	**1 (5)**

Diabetes & Hypertension were the most common co-morbid illnesses seen in both group of patients. Table 3 shows the number of patients with comorbid illness in both groups.

Table No. 3. Number of patients with co-morbid illness in each group.

Disease	**Familial PD** **n (%)**	**Sporadic PD** **n (%)**
Diabetes	5 (25)	3 (15)
Hypertension	4 (20)	4 (20)

There was no significant difference in the demographic features, clinical characteristics & medication doses between Familial & Sporadic PD patients. Table 4 highlights the comparison of above mentioned features in both groups.

Table No.4. Comparison of clinical features between Familial & Sporadic PD patients

Clinical feature	**Familial PD (n=20) Mean ± SD**	**Sporadic PD (n=20) Mean ± SD**	**p value**
Age of onset (yrs)	46.8 ± 10	48.75 ± 7.9	0.41
Duration of motor symptom (yrs)	6.2 ± 3.2	7.7 ± 4	0.3
L-dopa equivalent dose (mg)	447.5 ± 216.1	589.5 ± 321.7	0.11
L-dopa daily dose (mg)	227.5 ± 172	374.7 ± 245.6	**0.035**
DA in L-dopa equi dose (mg)	181.7 ± 172.7	190.5 ± 172.4	0.86
Rasagiline daily dose (mg)	0.15 ± 0.36	0 ± 0	0.42

Trihexyphenydyl daily dose (mg)	1.7 ± 2.6	1.05 ± 1.9	0.6
Amantadine daily dose (mg)	15 ± 67	65 ± 103.9	0.2
Escitalopram daily dose (mg)	2 ± 3.4	3.7 ± 4.8	0.38
Clonazepam daily dose (mg)	0.12 ± 0.3	0.05 ± 0.15	0.77
H & Y stage	2.12 ± 0.5	2.22 ± 0.44	0.56

Sleep symptomatology- sleep scales:

There was no significant difference with respect to PDSS total score & ESS total score between the two groups of PD. However, individual PDSS item analysis showed higher mean scores of PDSS item 9 & 12 in Familial PD compared to Sporadic group suggesting lesser impairment in Familial PD patients as highlighted in Table 5.

Table No. 5. Comparison of questionnaire items between Familial & Sporadic PD patients

Questionnaire item	**Familial PD (n=20) Mean ± SD**	**Sporadic PD (n=20) Mean ± SD**	**p value**
PDSS total score	108.9 ± 29.1	108.1± 21.8	0.71
PDSS 1	7 ± 2.3	6.2 ± 2.3	0.35
PDSS 2	7.6 ± 3.6	7.8 ± 2.4	0.67
PDSS 3	5.7 ± 4	5.5 ± 2.8	0.36
PDSS 4	7.8 ± 3.7	7.2 ± 2.8	0.18
PDSS 5	6.8 ± 4.1	8.1 ± 2.7	0.64
PDSS 6	8 ± 2.7	7.3 ± 3.1	0.47
PDSS 7	8.6 ± 2.8	9.1 ± 2.1	0.73
PDSS 8	4 ± 4.4	6.2 ± 2.7	0.2
PDSS 9	9.3 ± 1.4	6.7 ± 3.8	**0.04**
PDSS 10	7.3 ± 4	7.3 ± 2.8	0.56

PDSS 11	8.2 ± 2.6	6.3 ± 3.2	0.06
PDSS 12	9.5 ± 1.7	7.3 ± 3	**0.02**
PDSS 13	6.4 ± 4.4	7.7 ± 2.8	0.58
PDSS 14	6.3 ± 4.1	7.5 ± 3	0.52
PDSS 15	6.0 ± 4.3	8.1 ± 3.3	0.16
ESS total score	6.6 ± 3.7	5.5 ± 5.4	0.18

Sleep disturbances on PSG:

The overall prevalence of any sleep disturbance on PSG in **Familial PD** patients was **80%** & **Sporadic PD** patients was **90%**. There was no significant difference in the prevalence of SDB, sleep fragmentation & periodic limb movements between the two groups. Table 6 shows the prevalence of different PSG quantified sleep disturbances in Familial & Sporadic PD patients.

Table No. 6. Prevalence of sleep disturbances in Familial & Sporadic PD patients.

Sleep disturbance	Familial PD n (%)	Sporadic PD n (%)
Overall	**16 (80)**	**18 (90)**
SDB	**6 (30)**	**8 (40)**
Sleep fragmentation	**14 (70)**	**15 (75)**
PLM	**10 (50)**	**9 (45)**

PSG quantified sleep parameters & indices showed lower mean AHI & mean nocturnal oxygen desaturation in Familial PD patients than Sporadic ones as shown in Table 7.

Table No. 7. Comparison of PSG parameters between Familial & Sporadic PD patients

Parameter	**Familial PD (n=20) Mean ± SD**	**Sporadic PD (n=20) Mean ± SD**	**p value**
Sleep latency (min)	10.3 ± 13.3	4.7 ± 3.8	0.1
Total sleep time (min)	348.9 ± 54.4	327.6 ± 66.3	0.36
Duration Stage I sleep (min)	59.8 ± 42	53 ± 34.9	0.65
Duration Stage 2 sleep (min)	194.6 ± 55.7	182.7 ± 53.8	0.49
Duration Slow wave sleep (min)	50.5 ± 38.4	46 ± 35.4	0.86
Duration REM sleep	43.9 ± 23.5	45.8 ± 38.7	0.67

Sleep efficiency (%)	81.1 ± 9.5	82.5 ± 8	0.69
Apnea hypopnea index (AHI)	3.8 ± 6.5	7.9 ± 8.5	**0.02**
Snoring index	3.2 ± 7.6	7.5 ± 9.6	0.22
Max O2 desaturation (%)	88.4 ± 8.4	84.8 ± 5.3	**0.005**
Arousal index (AI)	20.1 ± 13.9	25.4 ± 15.6	0.25
PLMI	6.9 ± 9.7	12.4 ± 20.7	0.96

No parasomnias including **REM sleep behaviour disorder (RBD)** were noted in any patient.

DISCUSSION

This is the first study to compare the pattern of sleep dysfunction in two etiological subtypes of PD - Familial vs Sporadic.

The prevalence of PSG-quantified sleep disturbances in our patients with PD was 80-90%, which is comparable to previous studies in Sporadic PD in other population groups (15, 32, 33). There are no studies of sleep disturbances in Familial PD. Our study compared nocturnal as well as daytime sleep dysfunction using sleep scales and PSG in Familial & Sporadic PD patients.

There was no significant difference between the two groups with respect to age of onset, disease duration, clinical subtype, disease severity, comorbid illness, levodopa equivalent dose & other non-PD medications. Previous studies highlighted the importance of all above mentioned factors in producing sleep disturbances (25). Though the

mean L-dopa daily dose was lower in Familial PD patients, there was no significant difference in L-dopa equivalent dose between the two groups indicating no significant difference in the total dose of dopaminergic medications.

There was no significant difference in nocturnal sleep problems & daytime somnolence between the two groups as reflected in comparable total PDSS & ESS scores. However, in our study, **PDSS item 9 & 12** scores were significantly higher in familial PD patients implying **milder degree of symptoms attributable to nocturnal akinesia and early morning dystonia** than sporadic group.

The overall prevalence of sleep disturbances on PSG were not different between the two groups. Also basic quantitative & qualitative sleep parameters like sleep latency, total sleep time, sleep efficiency & duration of individual sleep stages (NREM & REM) were comparable.

Previous studies showed high prevalence of SDB in Sporadic PD patients which was comparable to our prevalence in both Sporadic & Familial cases (54). However, **SDB severity (reflected in mean AHI & nocturnal O2 desaturation) was less in Familial PD patients compared to Sporadic cases**. The pathogenesis of sleep apnea is complex but the central regulation from medullary centres is postulated. Whether the difference in severity of SDB could be due to difference in the pattern of involvement of brainstem centres in two subtypes of PD requires further studies.

The prevalence & severity of sleep fragmentation & PLM on PSG were not significantly different between the two groups, so also, the insomnia & nocturnal restlessness subitems on PDSS. However, the percentage of patients having sleep fragmentation & PLM were high in both the groups, as previously seen in many studies on Sporadic PD (23, 89).

Study limitations & strengths:-

This study has few limitations.

1. Sample size was small.
2. Many patients had PSG detected sleep disturbances without corresponding symptoms measured by PDSS & ESS which could be ascribed to the 1st night effect.

This study has its own strengths.

1. It is the 1st study to look for sleep disturbances in Familial PD & to compare the same with Sporadic groups.
2. Both groups were adequately matched for disease & drug related factors likely to influence outcome.

CONCLUSION

1. ***Sleep disturbances are common in both Familial & Sporadic PD patients.***

2. ***No difference in overall nocturnal & daytime sleep symptomatology except less severe nocturnal akinesia & morning dystonia in Familial group.***

3. ***PSG showed less severe sleep apnea in Familial PD patients.***

4. ***This may arise from differences in the pathophysiological processes affecting brainstem***

centres in the two forms of the disease. However larger studies are needed.

References

1. Parkinson J. An Essay on the Shaking Palsy. London: Whittingham and Rowland for Sherwood, Neely and Jones; 1817.
2. Forno LS. Neuropathology of Parkinson's disease. J Neuropathol Exp Neurol 1996;55:259 –272.
3. Weiner WJ. There is no Parkinson disease. Arch Neurol. 2008;65(6):705-708.
4. Thomas Gasser. Update on the Genetics of Parkinson's Disease. Mov Disord 2007;22. S343-350.
5. Polymeropoulos MH, Laveden C, Leroy E, et al. Mutation in the alpha synuclein gene identified in families with Parkinson's disease. Science 1997; 276;2045-7.
6. Kitada T, Asakawa S, Hattori N, et al. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature 1998; 392: 605-8.
7. Bonifati V, Rizzu P, van Baren MJ, et al. Mutations in the DJ-1 gene associated with autosomal recessive early onset parkinsonism. Science 2003; 299: 256-9.
8. Valente EM, Abou- Sleiman PM, Caputo V, et al. Hereditary early onset Parkinson's disease caused by mutations in PINK1. Science 2004; 304: 1158-60.
9. Paisan-Ruiz C, Jain S, Evans EW, et al. Dardarin mutations in Park 8 PD. Neuron 2004;44: 595-600.
10. Ramirez A, Heimbach A, Grundemann J, et al. Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. Nat Genet. 2006;38(10):1184-1191.

11. Zarranz JJ, Alegre J, Gomez-Esteban JC, et al. The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. Ann Neurol. 2004;55(2):164-173.
12. R H Madegowda, A Kishore, A Anand. Mutational screening of the parkin gene among South Indians with early onset Parkinson's disease. JNNP 2005; 76: 1588-90.
13. Punia S, Behari M, Govindappa ST, Swaminath PV, et al., Absence/rarity of commonly reported LRRK2 mutations in Indian Parkinson's disease patients. Neurosci Lett. 2006 Dec 1;409(2):83-8.
14. Vijayan B, Gopala S, Kishore A. LRRK2 G2019S mutation does not contribute to Parkinson's disease in South India. Neurol India. 2011 Mar-Apr;59(2):157-60.
15. Tandberg E, Larsen JP, Karlsen K. Excessive daytime sleepiness and sleep benefit in Parkinson's disease: a community-based study. Mov Disord 1999; 14: 922–7.
16. Adler CH, Thorpy MJ. Sleep issues in Parkinson's disease. Neurology 2005;64 (Suppl 3):S12–S20
17. Ondo WG, Dat Vuong K, Khan H, Atassi F, Kwak C, Jankovic J. Daytime sleepiness and other sleep disorders in Parkinson's disease. Neurology 2001;57:1392–6.
18. Kumar S, Bhatia M, Behari M. Excessive daytime sleepiness in Parkinson's disease as assessed by Epsworth Sleepiness Scale (ESS). Sleep Med 2003;4:339–42.
19. Tan EK, Lum SY, Fook-Chong SMC, Teoh ML, Yih Y, Tan L, et al. Evaluation of somnolence in Parkinson's disease: comparison with age- and sex-matched controls. Neurology 2002;58:465–8.
20. Gjerstad MD, Aarsland D, Larsen JP. Development of daytime somnolence over time in Parkinson's disease. Neurology 2002;58:1544–6.

21. Gjerstad MD, Alves G, Wentzel-Larsen T, Aarsland D, Larsen JP. Excessive daytime sleepiness in Parkinson's disease. Is it the drugs or the disease? Neurology 2006;67:853–8.
22. Chaudhuri KR. Nocturnal symptom complex in PD and its management. Neurology 2003; 61 (Suppl. 3): S17–S23.
23. Wetter TC, Collado-Seidel V, Pollmacher T, Yassouridis A, Trenkwalder C. Sleep and periodic leg movement patterns in drug-free patients with Parkinson's disease and multiple system atrophy. Sleep 2000;23:361–367.
24. Dhawan V, Healy DG, Pal S, Chaudhuri KR. Sleep related problems of Parkinson's disease. Age and Ageing 2006; 35: 220–228.
25. Kumar S, Bhatia M, Behari M. Sleep disorders in Parkinson's disease. Mov Disord 2002;17:775–781.
26. Braak H, Del Tredici K, Rüb U *et al*. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003; 24: 197–210.
27. Okubadejo NU. An analysis of genetic studies of Parkinson's disease in Africa. Parkinsonism and Related Disorders 14 (2008) 177–182.
28. Di Monte DA. The environment and Parkinson's disease: is the nigrostriatal system preferentially targeted by neurotoxins? Lancet Neurol 2003;2:531–538.
29. Elbaz A, Clavel J, Rathouz PJ, Moisan F, Galanaud JP, Delemotte B, Alperovitch A, Tzourio C. Professional exposure to pesticides and Parkinson disease. Ann Neurol 2009;66:494–504.
30. Quinn N, Critchley P, Marsden CD. Young onset Parkinson's disease. Mov Disord 1987; 2: 73–91.

31. Schrag A, Ben-Shlomo Y, Marsden CD, Quinn N. Young-onset Parkinson's disease – clinical features, natural history, and mortality. Mov Disord 1998; 13: 885–94.
32. Lees AJ, Blackburn NA, Campbell VL. The nighttime problems of Parkinson's disease. Clin Neuropharmacol 1988; 11: 512–9.
33. Oerlemans WG, de Weerd AW. The prevalence of sleep disorders in patients with Parkinson's disease: A self-reported, community-based survey. Sleep Med. 2002;3: 147-149.
34. Tandberg E, Larsen JP, Karlsen K. A community-based study of sleep disorders in patients with Parkinson's disease. Mov Disord 1998;13:895–9.
35. Shulman LM, Taback RL, Rabinstein AA, Weiner WJ. Non-recognition of depression and other non-motor symptoms in Parkinson's disease. Parkinsonism Relat Disord. 2002 Jan;8(3):193-7.
36. Chaudhuri KR, Pal S, DiMarco A, Whately-Smith C, Bridgman K, Mathew R, Pezzela FR, Forbes A, Hogl B, Trenkwalder C (2002) The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. J Neurol Neurosurg Psychiatry 73:629–635.
37. Abe K, Hikita T, Sakoda S. Sleep disturbances in Japanese patients with Parkinson's disease -comparing with patients in the UK. J Neurol Sci 2005;234:73–8.
38. Wang G, Cheng Q, Zeng J, Bai L, Liu GD, Zhang Y, Tan YY, Pan J, Hong Z, Wang Y, Chen SD. Sleep disorders in Chinese patients with Parkinson's disease: validation study of a Chinese version of Parkinson's disease sleep scale. J Neurol Sci. 2008 Aug 15;271(1-2):153-7.

39. Margis R, Donis K, Schonwald SV, Fagondes SC, Monte T, Martín-Martínez P, Chaudhuri KR, Kapczinski F, Rieder CR. Psychometric properties of the Parkinson's Disease Sleep Scale--Brazilian version. Parkinsonism Relat Disord. 2009 Aug;15(7):495-9.
40. Uemura Y, Nomura T, Inoue Y, Yamawaki M, Yasui K, Nakashima K. Validation of the Parkinson's disease sleep scale in Japanese patients: A comparison study using the Pittsburgh Sleep Quality Index, the Epworth Sleepiness Scale and Polysomnography. J Neurol Sci. 2009 Oct 3.
41. Martínez-Martín P, Salvador C, Menendez-Guisasola L, González S, Tobías A, Almazán J, Chaudhuri KR. Parkinson's Disease Sleep Scale: validation study of a Spanish version. Mov Disord. 2004 Oct;19(10):1226-32.
42. Ferini-Strambi L, Franceschi M, Pinto P, Zucconi M, Smirne S. Respiration and heart rate variability during sleep in untreated Parkinson patients. Gerontology 1992;38:92–98.
43. Diederich NJ, Vaillant M, Mancuso G, Lyen P, Tiete J. Progressive sleep 'destructuring' in Parkinson's disease. A polysomnographic study. Sleep Med 2005;6:313–8.
44. Dhawan V, Dhoat S, Williams AJ, Dimarco A, Pal S, Forbes A, Tobías A, Martinez-Martin P, Chaudhuri KR. The range and nature of sleep dysfunction in untreated Parkinson's disease (PD). A comparative controlled clinical study using the Parkinson's disease sleep scale and selective Polysomnography. J Neurol Sci. 2006 Oct 25;248(1-2):158-62.
45. Arnulf I, Konofal E, Merino-Andreu M, Houeto JL, Mesnage V, Welter MI, et al. Parkinson's disease and sleepiness. An integral part of PD. Neurology 2002;58:1019–24.
46. Hogl BE, Gomez-Arevalo G, Garcia S, Scipioni O, Rubio M, Blanco M, et al. A clinical, pharmacologic, and polysomnographic study of sleep benefit in Parkinson's disease. Neurology 1998;50:1332–9.

47. Roth T, Rye DB, Boerchet LD, Bartlett C, Bliwise DL, Cantor C, et al. Assessment of sleepiness and unintended sleep in Parkinson's disease patients taking dopamine agonists. Sleep Med 2003;4:275–80.
48. Maria B, Sophia S, Michalis M, Charalampos L, Andreas P, John ME, et al. Sleep breathing disorders in patients with idiopathic Parkinson's disease. Respir Med 2003;97:1151–7.
49. Gagnon J.F, Bédard MA, Fantini M.L et al. REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. Neurology 2002;59:585–589.
50. Eisensehr I, von Lindeiner H, Ja¨ger M, Noachtar S. REM sleep behavior disorder in sleep-disordered patients with versus without Parkinson's disease: is there a need for polysomnography? J Neurol Sci 2001; 186:7–11.
51. Wetter TC, Trenkwalder C, Gershanik O, Hogl B. Polysomnographic measures in Parkinson's disease: a comparison between patients with and without REM sleep disturbances. Wien Klin Wochenschr 2001; 113:249–253.
52. Diederich NJ, Vaillant M, Leischen M *et al*. Sleep apnoea syndrome in Parkinson's disease. A case-control study in 49 patients. Mov Disord 2005; 20: 1413–8.
53. Young A, Home M, Churchward T, Freezer N, Holmes P, Ho M. Comparison of sleep disturbance in mild versus severe Parkinson's disease. Sleep 2002;25:573–577.
54. M.I. Norlinah , K. Nor Afidah , A.T. Noradina , A.S. Shamsul , B.B. Hamidon , R. Sahathevan ,A.A. Raymond. Sleep disturbances in Malaysian patients with Parkinson's disease using polysomnography and PDSS. Parkinsonism and Related Disorders (2009).

55. Schenck CH, Bundlie SR, Mahowald MW. Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder. Neurology 1996; 46: 388–93.

56. MacMahon D. Why excessive daytime sleepiness is an important issue in Parkinson's disease. Adv Clin Neurol Rehabil 2005; 5: 46–9.

57. Rye DB, Jankovic J. Emerging views of dopamine in modulating sleep/wake state from an unlikely source: PD. Neurology 2002; 58: 341–6.

58. Saper CB et al. The sleep switch: the hypothalamic control of sleep and wakefulness. Trends Neurosci 2001; 24: 726–31.

59. Nishino S, Ripley B, Overseem S et al. Hypocretin (orexin) deficiency in human narcolepsy. Lancet 2000; 355: 39–40.

60. Ripley B, Overseem S, Fujuki N et al. CSF hypocretin/orexin levels in narcolepsy and other neurological conditions. Neurology 2001; 57: 2253–8.

61. Kru¨ger R, Kuhn W, Mu¨ller T, et al. Ala39Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. Nat Genet 1998;18: 106–108.

62. Zarranz JJ, Alegre J, Gomez-Esteban JC, et al. The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. Ann Neurol 2004;55:164 –173.

63. Berg D, Niwar M, Maass S, et al. Alpha-synuclein and Parkinson's disease: implications from the screening of more than 1,900 patients. Mov Disord 2005;20:1191–1194.

64. Goedert M, Spillantini MG, Davies SW. Filamentous nerve cell inclusions in neurodegenerative diseases. Curr Opin Neurobiol 1998;8:619–632.

65. Singleton AB, Farrer M, Johnson J, et al. alpha -Synuclein locus triplication causes Parkinson's disease. Science 2003;302:841.

66. Ibanez P, Bonnet AM, Debarges B, et al. Causal relation between alpha-synuclein gene duplication and familial Parkinson's disease. Lancet 2004;364:1169 –1171.

67. Golbe LI, Di Iorio G, Bonavita V, Miller DC, Duvoisin RC. A large kindred with autosomal dominant Parkinson's disease. Ann Neurol 1990;27:276 –282.

68. Spira PJ, Sharpe DM, Halliday G, Cavanagh J, Nicholson GA. Clinical and pathological features of a Parkinsonian syndrome in a family with an Ala53Thr alpha-synuclein mutation. Ann Neurol 2001;49:313–319.

69. Funayama M, Hasegawa K, Kowa H, Saito M, Tsuji S, Obata F. A new locus for Parkinson's disease (PARK8) maps to chromosome 12p11.2– q13.1. Ann Neurol 2002;51:296 –301.

70. Zimprich A, Biskup S, Leitner P, et al. Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. Neuron 2004;44:601– 607.

71. Paisan-Ruiz C, Jain S, Evans EW, et al. Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. Neuron 2004;44:595– 600.

72. Berg D, Schweitzer K, Leitner P, et al. Type and frequency of mutations in the LRRK2 gene in familial and sporadic Parkinson's disease. Brain 2005;128:3000 –3011.

73. Shimura H, Hattori N, Kubo S, et al. Familial Parkinson disease gene product, parkin, is a ubiquitin–protein ligase [In Process Citation]. Nat Genet 2000;25:302–305.

74. Valente EM, Salvi S, Ialongo T, et al. PINK1 mutations are associated with sporadic early-onset parkinsonism. Ann Neurol 2004;56:336 –341.

75. Hatano Y, Li Y, Sato K, et al. Novel PINK1 mutations in early onset parkinsonism. Ann Neurol 2004;56:424–427.

76. Rogaeva E, Johnson J, Lang AE, et al. Analysis of the PINK1 gene in a large cohort of cases with Parkinson disease. Arch Neurol 2004;61:1898 –1904.

77. Rohe CF, Montagna P, Breedveld G, Cortelli P, Oostra BA, Bonifati V. Homozygous PINK1 C-terminus mutation causing early-onset parkinsonism. Ann Neurol 2004;56:427– 431.

78. Healy DG, Abou-Sleiman PM, Valente EM, et al. DJ-1 mutations in Parkinson's disease. J Neurol Neurosurg Psychiatry 2004;75: 144–145.

79. Hedrich K, Djarmati A, Schafer N, et al. DJ-1 (PARK7) mutations are less frequent than Parkin (PARK2) mutations in early-onset Parkinson disease. Neurology 2004;62:389 – 394.

80. Leroy E, Boyer R, Auburger G, et al. The ubiquitin pathway in Parkinson's disease [letter]. Nature 1998;395:451– 452.

81. Gasser T, Mu¨ller-Myhsok B, Wszolek ZK, et al. A susceptibility locus for Parkinson's disease maps to chromosome 2p13. Nat Genet 1998;18:262–265.

82. Hedrich K, Eskelson C, Wilmot B, et al. Distribution, type & origin of Parkin mutations: Review & case studies. Mov Disord 2004; 19: 1146-57.

83. Tuin I, Voss U, Kessler K, et al. Sleep quality in a family with hereditary parkinsonism (PARK6). Sleep Med 2008; 9: 684-688.

84. Juan J, Anabel F, et al. Abnormal Sleep Architecture Is an Early Feature in the E46K Familial Synucleinopathy. Mov disord 2005; 20: 1310–1315.

85. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–184.

86. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991; 14: 540–5.

87. Noradina AT, Hamidon BB, Roslan H, Raymond AA. Risk factors for developing sleep-disordered breathing in patients with recent ischaemic stroke. Singapore Med J 2006;47:392–9.

88. American Academy of Sleep Medicine. International Classification of Sleep Disorders. 2nd ed. Diagnostic & coding manual, revised. Westchester, IL (US): American Academy of Sleep Medicine; 2005.

89. Gjerstad MD, Wentzel-Larsen T, Aarsland D, Larsen JP. Insomnia in Parkinson's disease: frequency and progression over time. J Neurol Neurosurg Psychiatry 2007;78:476–9.

Appendix

STUDY PROFORMA

1. Patient's details and history:

Name:

Hospital no:

Age: Level of Education:

Socioeconomic status: Marital status:

Address:

Telephone No:

Duration of First Symptom: Age at onset:

Type of Parkinson's Disease: Tremor Dominant / Rigid Bradykinetic / Mixed

Other medical illnesses:

Family History of PD:

No of family members affected:

Pedigree chart:

Other relevant family history:

RLS

Depression

2. Details of Medications

Present Medications	***Total Daily Dose***	***Duration of Exposure***	***Dosing Schedule***
L-dopa			
Entacapone			
Pramipexole			
Ropinirole			
Trihexiphenydyl			
Amantadine			
Rasagiline			
Antidepressants (specify)			
Antipsychotics (specify)			
Hypnotics/ Anxiolytics (specify)			
Others (specify)			

3. Clinical Examination:

BMI: kg/m2

UPDRS part III: (Specify whether "on" / "off")

Speech: Facial expression:

Rest Tremor: Face and lips:

Limbs: RUL- RLL- LUL- LLL -

Postural Tremor: RUL- LUL-

Rigidity: Neck-

Limbs: RUL- RLL- LUL- LLL –

Hand Grips: Rt- Lt-

Finger taps: Rt- Lt-

Rapid Alternating Movements: Rt- Lt-

Leg agility: Rt- Lt-

Rising from chair- Posture- Gait- Postural stability- Body bradykinesia-

Total score (UPDRS III)-

Hoehn & Yahr stage:

4. Sleep Questionnaire

Parkinson's Disease Sleep Scale: Score

Q:1

Q:2

Q:3

Q:4

Q:5

Q:6

Q:7

Q:8

Q:9

Q:10

Q:11

Q:12

Q:13

Q:14

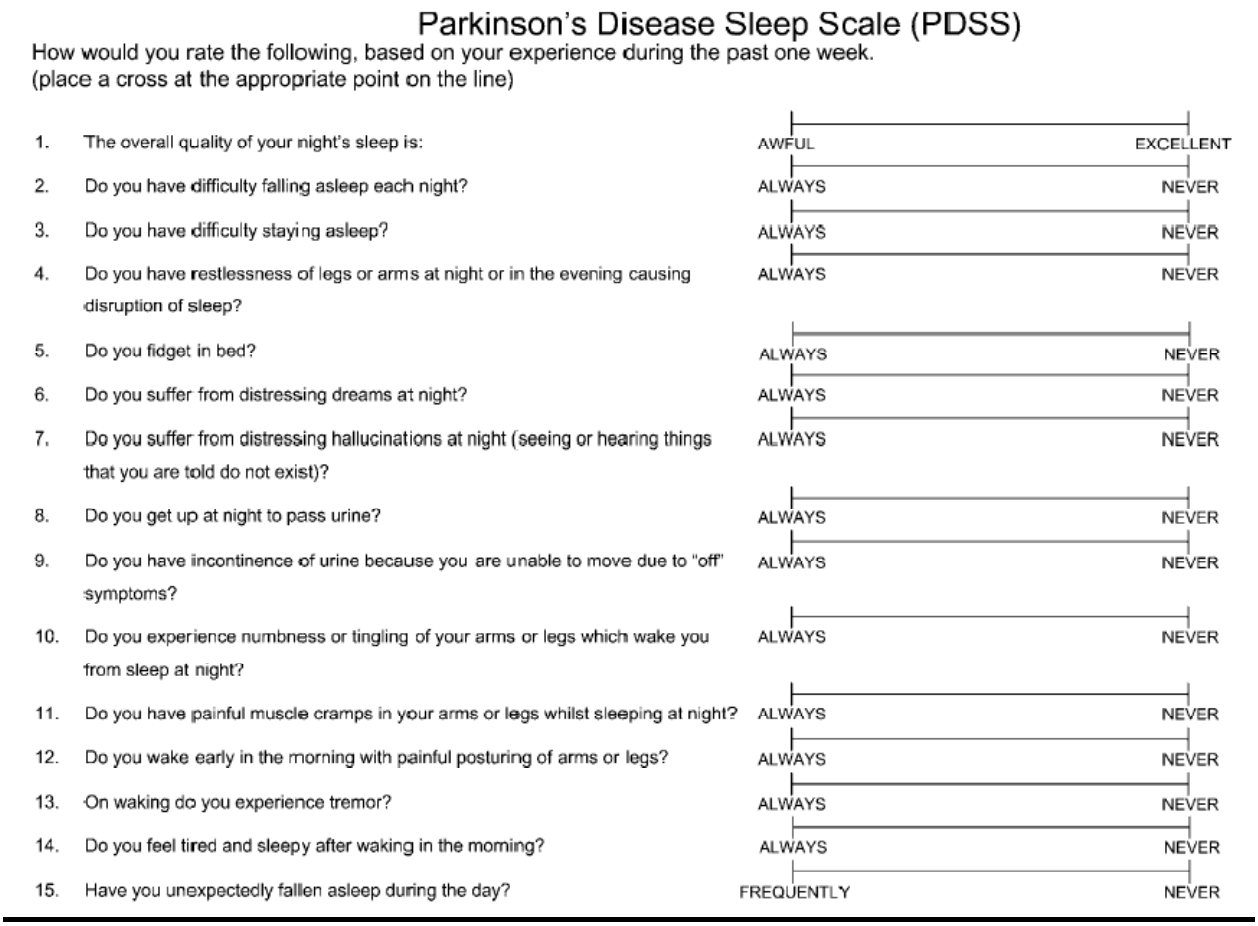
Q:15

Total PDSS Score:

Epworth Sleepiness Score:

5. Polysomnography (PSG) findings:

- total sleep time (TST)
- sleep latency (duration to sleep onset)
- sleep efficiency (percentage of total sleep duration over total time in bed)
- duration of Stage 1, 2, slow wave & REM sleep
- apnoea–hypopnoea index (AHI)
- apnea severity
- arousal index (AI)
- periodic limb movement index (PLMI)
- periodic limb movement severity



Parkinson's Disease Sleep Scale (PDSS)

How would you rate the following, based on your experience during the past one week.
(place a cross at the appropriate point on the line)

1.	The overall quality of your night's sleep is:	AWFUL	EXCELLENT
2.	Do you have difficulty falling asleep each night?	ALWAYS	NEVER
3.	Do you have difficulty staying asleep?	ALWAYS	NEVER
4.	Do you have restlessness of legs or arms at night or in the evening causing disruption of sleep?	ALWAYS	NEVER
5.	Do you fidget in bed?	ALWAYS	NEVER
6.	Do you suffer from distressing dreams at night?	ALWAYS	NEVER
7.	Do you suffer from distressing hallucinations at night (seeing or hearing things that you are told do not exist)?	ALWAYS	NEVER
8.	Do you get up at night to pass urine?	ALWAYS	NEVER
9.	Do you have incontinence of urine because you are unable to move due to "off" symptoms?	ALWAYS	NEVER
10.	Do you experience numbness or tingling of your arms or legs which wake you from sleep at night?	ALWAYS	NEVER
11.	Do you have painful muscle cramps in your arms or legs whilst sleeping at night?	ALWAYS	NEVER
12.	Do you wake early in the morning with painful posturing of arms or legs?	ALWAYS	NEVER
13.	On waking do you experience tremor?	ALWAYS	NEVER
14.	Do you feel tired and sleepy after waking in the morning?	ALWAYS	NEVER
15.	Have you unexpectedly fallen asleep during the day?	FREQUENTLY	NEVER

The patients are asked to mark their responses according to severity by placing a cross mark on the 10 cm line.

10 represents excellent/never responses; 0 represents the worst score.

Epworth Sleepiness Scale (ESS)

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times.

Situation	Would never doze 0	Slight chance of dozing 1	Moderate chance of dozing 2	High chance of dozing 3
Sitting & reading				
Watching TV				
Sitting inactive in a public place (eg, at the theatre or a meeting)				
As a passenger in a car for an hour without a break				
Lying down to rest in the afternoon when circumstances permit				
Sitting & talking to someone				
Sitting quietly after a lunch without alcohol				
In a car while stopped for a few minutes in traffic				

The scoring varies from 0 (no daytime somnolence) to 24 (severe daytime somnolence).

Modified Hoehn & Yahr staging for Parkinson's disease

Stage	Disease state
0	No signs of disease
1	Unilateral disease
1.5	Unilateral plus axial involvement
2	Bilateral disease, without impairment of balance
2.5	Mild bilateral disease with recovery on pull test
3	Mild to moderate bilateral disease; some postural instability; physically independent
4	Severe disability; still able to walk or stand unassisted
5	Wheelchair bound or bedridden unless aided

L-dopa equivalent dose calculation:

Conversion factors

Drug	Conversion factor
Immediate release L-dopa	X 1
Controlled release L-dopa	X 0.75
Entacapone	LD x 0.33
Tolcapone	LD x 0.5
Pramipexole	X 100
Ropinirole	X 20
Rotigotine	X 30
Selegiline-Oral	X 10
Selegiline – sublingual	X 80
Rasagiline	X 100
Amantadine	X 1
Apomorphine	X 10