



RESEARCH ARTICLE

CLINICAL ASSESSMENT OF NON MOTOR SYMPTOMS IN PARKINSON'S DISEASE

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ABSTRACT

**Introduction:** Parkinson's Disease is an age related extra pyramidal neurological manifestation resulting in motor impairment. The scope of non motor symptoms in Parkinson's disease has been explored in depth in recent times. Several symptoms including sleep disorders, anxiety, olfactory dysfunction, visual impairment etc are often ignored. This study aims to evaluate the magnitude of non motor symptoms among the patients with Parkinson's disease.

**Methodology:** This hospital based study was carried out among 150 patients diagnosed with Parkinson's Disease visiting the tertiary care center. The patients were grouped as treated and drug naïve. All the patients were evaluated for cognitive functions, sleep, olfactory, visual, anxiety, etc using appropriate scales. Independent samples t test and ANOVA was used to analyze the statistical significance between the variables using SPSS ver 16 software.

**Results:** Out of 150 total PD patients, 115 (76.7%) were males and 35 (23.3%) were females. The majority of the patients belonged to age group 61-70 years (n=69, 46%). The majority of the PD patients had duration of illness between 1 - 5years (n=97, 64.7%). The mean MDS-UPDRS scores (Part 1, 2, 3) were significantly lower in drug-naïve as compared to treated PD patients

**Conclusion:** This study has thrown light on the magnitude of the non motor symptoms among patients with Parkinson's disease. This study has also effectively helped in sub typing the non motor symptoms.

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INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder, after Alzheimer's disease (Przedborski, 2007). In community-based series, PD accounts for more than 80% of all Parkinsonism, with a prevalence of approximately 360 per 100,000 and an incidence of 18 per 100,000 per year (De Lau, 2006). Among the subjects with Parkinsonism visiting the movement disorder clinics, approximately 80-85% have PD, with the rest belonging to the categories of secondary Parkinsonism (Mitra et al., 2003; Behari et al., 1999) in their study reported that about 1% of population above the age of 65 years and about 5% above the age of 80 years suffer from PD (Behari et al., 1999). As early as 1817 James Parkinson in his monograph, The Shaking Palsy (1817) described the nonmotor symptoms (NMS) of PD such as sleep disturbance, constipation, dysarthria, dysphonia, dysphagia, sialorrhoea, and urinary incontinence which were not given importance in clinical practice (Parkinson, 1817; Chaudhuri et al., 2016).

symptoms are frequent accompaniments of PD leading to significant impairment in quality of life, and frequent hospitalization (Schrag et al., 2000; Hely et al., 2005; Aarsland et al., 2000; Chaudhuri et al., 2005). NMSs in PD have been systematically described for the first time in 2006 by Chaudhuri et al. (2006) Prevalence of NMS is reported to be in upto 21% at the time of diagnosis and increases up to 88% after 7 years of disease progression (O'Sullivan, 2008). In conjunction with motor symptoms, NMS also play an important role in PD throughout the course of the disease. Some of them, such as depression, fatigue, and olfactory disorders, may appear at the earliest stage of the disease, in drug naïve patients (Grosset et al., 2007). NMS can even precede the motor symptoms or signs by several years and then herald the onset of PD. These premotor symptoms include olfactory dysfunction, REM sleep behaviour disorder (RBD), constipation, depression, and pain (Tolosa et al., 2009). Autonomic dysfunction such as orthostatic hypotension, constipation and incontinence are common in neurodegenerative diseases, particularly PD but its relevance as a preclinical marker for PD and dementia is not well studied. In patients with advanced PD, NMS coexist for most patients with motor fluctuations with its frequency increasing along with the disease duration (Witjas et al., 2002; Barone et al., 2009).

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Sleep disorders are among the most frequent non-motor problems of PD (Tandberg *et al.*, 1998). They include difficulties falling asleep, frequent awakenings, nocturnal cramping, painful dystonia, or nocturnal motor symptoms with difficulties turning in bed, restless legs syndrome (RLS), nighttime incontinence, nocturnal hallucinations, and daytime sleepiness (Poewe *et al.*, 2007). Kumar *et al.*, 2002 in a study found out the prevalence of sleep related problems like insomnia (32%), nightmares (32%) and excessive day time sleepiness (15%) in PD and concluded that sleep problems are common in PD than in control ( $p < 0.001$ ) (Kumar *et al.*, 2002). Olfactory dysfunction (OD) may affect up to 90% of PD patients and has been described as a preclinical marker (Doty). Studies have reported olfactory deficits in asymptomatic relatives of patients with PD, some of whom subsequently became symptomatic. Visual problems during the course of the disease like alterations in visual acuity, contrast sensitivity, colour discrimination, pupil reactivity, eye movements, motion perception, visual field sensitivity, and visual processing speeds have been reported in PD patients (Matsui *et al.*, 2006). In addition, there may be disturbances of visuo-spatial orientation, facial recognition problems, and chronic visual hallucinations (Matsui *et al.*, 2006 Diederich *et al.*, 2002).

**Objectives:** To clinically evaluate the non motor symptoms in Parkinson's Disease

## MATERIALS AND METHODS

**Study Setting:** This study was carried out as a hospital based cross sectional study among patients With Parkinson's disease who who attended inpatient and outpatient Department of Neurology of Sree Balaji Medical College and Hospital, Chennai for a period of 10 months between February and September 2015.

**Sample size and sampling:** Based on intensive literature search, it was observed that sleepiness occurs in 59.4% of the patients with parkinson's disease (Hu *et al.*, 2011). This was taken up for calculating the sample size. At 95% level of significance and 15% relative precision, the sample size was estimated to be 117. Accounting 10% for non response, the sample size was calculated as 130. The final sample size was rounded off to 150. All the patients who visited the facility during the study period were taken up for the study by purposive sampling.

### Inclusion Criteria

- Only the consenting Patients were included for the study
- Patients confirming diagnosis of Parkinson's Disease according to
- United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria (Larsen *et al.*, 2004).
- Criteria of diagnosis of Parkinson disease (Gelb *et al.*, 1999) commissioned and supported by the Advisory Council of the National Institute of Neurological Disorders and Stroke, US National Institutes of Health
- Patients in all age groups was included for the study (drug naïve and on medication).
- Patients with MMSE (Mini Mental State Examination) (Folstein *et al.*, 1975) score of greater than 24 were included for the study.

- All the PD patients were staged according to Hoehn and Yahr Scale (Goetz *et al.*, 2004).

### Exclusion criteria

- All non-consenting patients were excluded.
- Patients who were unable to understand or answer questionnaires or had any co-morbidity or disorder interfering with or impeding assessment of PD manifestations were excluded.
- All drug induced PD and patients with history of drug intake like flunarasine and antipsychotic medications were excluded.
- Any Family history of psychosis and depression were also excluded.

**Ethical committee approval and informed consent:** Permissions from Institutional Ethics Committee was obtained prior to the data collection. All the patients were explained in detail about the study and informed consent was obtained prior to the data collection.

**Tools for Data Collection:** Detailed history was taken for all the patients followed by a thorough neurological examination. The following scales and scoring systems were used.

- Movement Disorders Society Sponsored Revision Of The Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[28] was used to determine the clinical severity after passing the certified course of MDS-UPDRS as per the rules of MDS.
- Comprehensive non-motor symptoms assessments
- Non-motorsymptomsquestionnaire(NMS-QUEST)
- Scale for the assessment of sleep related symptoms
- Parkinson Disease Sleep Scale 2 (PDSS2) (Chaudhur *et al.*, 2002)
- Epworth Sleepiness Scale(ESS) (Johns, 1991)
- REM Sleep Behaviour Disorders ( RBD) Rating Scale (Stiasny - Kolster *et al.*, 2007)
- Restless Leg Syndrome (RLS) International RLS scale (Barnes, 1989).
- Fatigue Severity Scale (FSS)
- Barnes Akathisia Rating Scale (BARS) (Barnes, 1989).

**Data analysis:** Demographic variables in categorical/dichotomous were given in frequencies with their percentages. Score was given in mean and standard deviation. Quantitative data was analyzed using Student independent t-test to find the significant difference between treated PD and Drug naïve PD. Qualitative data was analyzed using Chi square test to find the significant difference between treated PD and Drug naïve PD. MDS-UPDRS PART III with MOCA, MMSE, RBD. Correlation was analyzed using Karl Pearson correlation method. For analysis of data Statistical Package for the Social Sciences (SPSS), version 16.0, EPI INFO version 3.5.1 were used.  $p < 0.05$  was considered statistically significant.

## RESULTS

In the present study out of total 150 PD patients, 120 were treated patients and 30 were drug-naïve patients. Out of 150 total PD patients, 115 (76.7%) were males and 35 (23.3%) were females.

**Table 1. Background characteristics of the study participants**

S. No	Characteristics	Frequency N=150	Percentage
1	Sex		
	Male	115	76.7
	Female	35	23.3
2	Age(years)		
	< 50	3	2
	51-60	30	20
	61-70	69	46
	71-80	37	24.7
	> 80	11	7.3
3	Duration of Illness		
	<1 year	15	10
	1 – 5 years	97	64.7
	6-10 years	24	16
	> 10 years	14	9.3

**Table 2. Treatment details of the study participants**

S. No.	Variables	Total PD Patients	Treated PD Patients	Drug naïve PD Patients
1	MDS-UPDRS score (mean ± SD)			
	Part1	11.48±8.02	12.80±8.06	6.20±5.28
	Part2	12.52±7.61	13.54±7.70	8.43±0.33
	Part3	33.66±16.74	35.54±16.15	26.13±17.22
	Part4	0.36±1.35	0.43±1.49	0.00±0.00
	Total Score	58.02 ± 33.62	62.31 ± 33.4	40.76 ± 22.83
2	Duration Of Illness (mean± SD)	4.54±4.21	5.30±4.76	1.50±1.19
3	Family History	7(4.7%)	7(5.8%)	0(0.0%)
4	Side Most Affected			
	Left	50(33.3%)	48(40.0%)	2(6.7%)
	Right	100(66.7%)	72(60.0%)	28(40.0%)
	Both(Symmetrical)	-	-	-
	Tremor	142(94.7%)	115(95.5%)	27(90.0%)
	Rigidity	150(100.0%)	120(100.0)	30(100.0%)
	Bradykinesia	150(100.0%)	120(100.0)	30(100.0%)
	Dystonia	42(28.0%)	40(33.3%)	2(6.7%)

**Table 3. Correlation of various non-motor scales with H&Y stage**

S. No	Scale	H & Y STAGE										ANOVA	
		1.0		2.0		2.5		3.0		4.0		F-test	P value
		Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D		
1	MOCA	27.57	1.85	25.84	2.23	25.50	1.38	24.33	2.30	24.60	1.34	12.49	0.0001
2	MMSE	28.33	1.36	27.02	1.59	26.50	1.17	25.48	1.67	25.80	2.05	17.08	0.0001
3	PDSS2	6.59	5.67	10.30	6.17	17.75	8.40	20.00	7.27	30.60	8.59	32.27	0.0001
4	ESS	5.29	2.52	7.61	2.91	9.08	2.64	10.85	2.16	14.20	3.03	28.14	0.0001
6	FSS	26.22	6.35	33.37	5.79	39.50	8.55	42.33	6.71	47.20	3.56	37.68	0.0001
7	RLS	0.59	1.74	0.26	1.30	5.17	5.20	2.96	5.04	8.20	6.83	14.93	0.0001
8	RBD	1.53	2.60	3.12	2.52	6.08	3.20	6.44	3.26	8.00	1.22	20.62	0.0001

**Table 4. Comparison of MDS –UPDRS with H&Y STAGE among the study participants**

S. No		H & Y STAGE										ANOVA	
		1.0		2.0		2.5		3.0		4.0		F-test	P value
		Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D		
1	PART I	4.80	4.59	10.11	4.96	16.67	5.90	21.00	6.18	23.40	8.05	52.06	0.0001
2	PART II	6.45	4.89	12.00	4.40	16.33	3.96	19.67	7.53	27.40	10.48	37.59	0.0001
3	PART III	20.20	10.61	31.54	11.27	40.25	7.17	51.48	13.76	57.40	25.36	36.87	0.0001
4	PART IV	0.14	1.00	0.30	1.10	1.08	2.54	0.37	1.33	3.40	3.51	6.98	0.0001

The majority of the patients belonged to age group 61-70 years (n=69, 46%). The majority of the PD patients had duration of illness between 1 - 5 years (n=97, 64.7%). The background details are given in Table 1. Table treatment details of the study participants. Majority of patients belonged to Stage I (n= 49, 32.7%), Stage 2 (n=57, 38%) and Stage 3 (n=27, 18%). The mean MDS-UPDRS scores (Part 1, 2, 3) were significantly lower in drug-naïve as compared to treated PD patients. This study included 7 familial PD patients. The comparison between the mean scores of non motors scales with H&Y staging is given in Table 3.

A significant decrease in the mean scores was observed with MOCA and MMSE while a statistically significant increase was observed with all the other scales. The observed difference was statistically significant (p=0.0001). The scores of MDS-UPDRS was compared with H&Y staging (Table 4). There was a significant difference observed with the increase in the staging and the observed difference was statistically significant (p=0.0001). The mean scores of the NMS scales among drug naïve and treated PD patients is given in Table 5. A statistically significant difference was observed with all the scales between the treated and drug naïve patients except MOCA and MMSE.

Table 5. Mean values of various NMS rating scales

S. No	Variable	Total PD Patients Mean(SD)	Treated PD patients (n=120)	Drug Naïve PD(n=30)	p value (Treated With Drug- Naïve)
1	MOCA	26.50(1.38)	26.00(2.40)	26.33(2.09)	0.48
2	MMSE	27.15(1.17)	27.06(1.82)	27.20(1.83)P=0.70	0.70
3	PDSS2	14.75(8.25)	13.34(9.16)	7.17(4.80)	0.001*
4	ESS	9.08(2.64)	8.12(3.61)	6.40(2.50)P=0.01*	0.01*
5	FSS	35.12(8.65)	34.48(9.23)	30.07(6.73)P=0.02*	0.02*
6	RLS	1.93(3.84)	1.83(3.93)	0.27(1.46)	0.05*
7	RBD	5.76(3.20)	4.10(3.39)	1.60(2.40)P=0.001***	0.001*

Table 6. Distribution of non-motor symptoms intreated &amp; drug-naïve PDpatients

S. No	Variables	Total PD patients (n=150)	Treated PD patients (n=120)	Drug naïve PD patients (n=30)	p value
		N (%)	N (%)	N (%)	
1	Dribbling saliva	41 (27.3)	32 (26.7)	9 (30)	0.01
2	Taste	49 (32)	42 (35.0)	7 (23.3)	0.01
3	Swallowing	51 (34)	41 (34.2)	10 (33.3)	0.01
4	Nausea	27 (18)	25 (20.8)	2 (6.7)	0.01
5	Constipation	77 (51.3)	76 (63.3)	1 (3.3)	0.01
6	Bowel incontinence	21 (14)	21 (17.5)	5 (16.7)	0.01
7	Bowel emptying incomplete	78 (52)	73 (60.8)	9 (30)	0.01
8	Urine urgency	82 (54)	73 (60.8)	7 (23.3)	0.01
9	Urine frequency at night	76 (50.7)	69 (57.5)	7 (23.3)	0.01
10	Unexplained pain	49 (32)	42 (35.0)	10 (33.3)	0.01
11	Weight loss	79 (52.7)	69 (57.5)	1 (3.3)	0.01
12	Loss of interest	33 (22)	32 (35.0)	18 (60)	0.01
13	Concentration	92 (61.3)	74 (57.5)	18 (60.0)	0.86
14	Mood	102 (68)	4 (35.0)	0 (0.0)	0.29
15	Sexual interest	16 (10.7)	16 (57.5)	1 (3.3)	0.03
16	Sexual difficulty	7 (4)	6 (26.7)	2 (6.7)	0.21
17	Postural fall	20 (13.3)	18 (61.7)	2 (6.7)	0.23
18	Falling	35 (23)	33 (70.0)	6 (20)	0.02
19	Distressing dreams	72 (48)	66 (13.3)	1 (3.3)	0.001
20	Swelling	10 (6)	9 (5.0)	2 (6.7)	0.41
21	Excessive Sweating	15 (10)	13 (15.0)	0 (0.0)	0.49
22	Double vision	6 (4)	6 (27.5)	10 (33.3)	0.21

This table inferred that when the mean scores of various NMS scales was compared between treated and drug naïve PD, there was a statistical significant difference noted in the mean value of PDSS2, ESS, FSS, RLS AND RBD. This means that the sleep disturbances, daytime sleepiness, fatigueness and depression were higher in treated PD patients. The distribution of non motor symptoms among the treated and drug naïve patients is given in Table 6. Statistical significance was observed with several symptoms like dribbling of saliva, taste, swallowing, etc.

## DISCUSSION

This study clinically evaluated the non motor symptoms among 150 patients with Parkinson's Disease. Out of the 150 patients (115 males and 35 females), 120 were treated patients and 30 were drug-naïve patients respectively. The demographic data (Table 1) of PD patients showed mean age of  $67.44 \pm 8.47$ , mean H&Y stage of  $1.95 \pm 0.81$  [H&Y stage 1 (32.7%) and stage 2 (38%)] and duration of illness was  $4.54 \pm 4.21$ . The mean MDS-UPDRS of the total PD Part I [Mentation, behaviour, and mood] ( $11.48 \pm 8.02$ ), Part II [Activities of daily life] ( $12.52 \pm 7.61$ ), Part III [Motor evaluation] ( $33.66 \pm 16.74$ ), Part IV [Complications of Therapy] ( $0.36 \pm 1.35$ ). The mean difference between the treated and the drug-naïve MDS-UPDRS score was statistically significant. The spectrum of NMS was assessed by NMS Quest. We found that the mean NMS symptoms were mood (68%), reduced concentration (61.3%), urinary urgency (54.7%), incomplete bowel emptying (52%), constipation (51.3%), increased urinary frequency (50.7%), dreams (48%), swallowing (34%), sensory symptoms like unexplained pain(32.7%) and hallucinations (30%).

Colour vision was assessed by Snellen's chart. Colour blindness was noted in 10% (n=16) of PD patients. Our study results were comparable with several studies (Barone *et al.*, 2009; Poewe, 2007; Deepti Vibha *et al.*, 2013). Most items of NMS Quest were satisfactorily answered. Certain questions of NMS Quest enquiring about sex drive and difficulty sex received maximum negative response. The reason for this maybe because the questions addressed to older population and were not sexually active, while some felt uncomfortable answering these questions. It was observed that most of the patients were having overlapping of multiple NMS. That means when one symptom is present it is mandatory to search for the other symptoms in the same patient without which there is high probability of missing the symptoms as these NMS symptoms are hidden problems. Along with all NMS, we have made an attempt to study the prevalence of sleep disorders like Excessive Daytime Sleepiness (ESS), REM behavior sleep disorders (RBD), Restless Leg Syndrome (RLS) and the overall Quality of sleep as assessed by ESS, RBD, RLS and PDSS2 rating scales respectively. It was noticed that as assessed by PDSS2, 86% (n=129) had bad quality of sleep, 82% (n=123) had lack of sleep refreshment, 78% (n=117) had difficulty in falling asleep, 74% (n=111) had difficulty in staying asleep and 76.6% (n=115) had disturbed sleep due to nocturia. Whereas other symptoms significantly affecting the sleep were cramps, sensory symptoms, distressing dreams, hallucinations and RLS like syndromes. From the present study we noticed that 28.66% (n=43) were having excessive daytime sleepiness out of which 26.66% (n=40) were having ESS score in the range of 10-15 and 2% (n=3) were having ESS >15. Our studies were similar to the below table studies (Kumar *et al.*, 2002; Birgit Hog *et al.*, 2003; Matthew *et al.*, 2003; Sanju *et al.*, 2014; Tanya Simuni *et al.*, 2015; ) except in

study by Paus *et al.* (2003) where there was 75% incidence of excessive daytime sleepiness using ESS Score ( $\geq 10$ ). In the present study we observed that 21.33% (n=32) patients had restless leg syndrome (RLS). Out of these, all the patients belonged to mild (n=24, 16%) and moderate (n=8, 5.3%) severity of RLS score. Also we have observed that 40.67% (n=61) patients had RBD problems (RBD Scale  $>5$ ). The mean RBD Score was statistically significant between the treated and drug naïve PD ( $4.10 \pm 3.39$  vs  $1.60 \pm 2.40$ ). It was also observed that as the disease progresses there was increase in the severity of RBD symptoms. We also observed that there is an increased occurrence of hallucinations (n=40, 65.57%) in PD patients with RBD and all the patients had poor overall sleep quality. This study was similar to the study by Madhuri Behari *et al.* (2013) observed higher frequency of hallucinations among RBD patients. Kee Hyung Park *et al.* (2016) observed that RBD patients had more sleep disturbances, lower sleep quality and more motor disability.

Along with these we attempted to separate patients with inner restlessness (akathisia) using Barnes Akathisia Rating Scale (BARS). Though BARS is designed for drug-induced akathisia, we have used this scale for assessing akathisia in PD and found it to be a useful scale in assessing akathisia. But in our study we have only 6 PD patients with akathisia (4%) out of which 2 (1.3%) belonged to H&Y stage 3 and 4 (2.6%) belonged to H & Y stage 4. While subtyping and analysing the various data of Non Motor Symptoms, factors like bowel (constipation, fecal incontinence) and bladder disturbances (urgency, frequency, incontinence) were excluded from autonomic symptoms as these symptoms can per se be attributed to multifactorial causes like drugs (anticholinergic), benign prostrate hypertrophy (BPH), old age etc. Previous study by Van Rooden *et al.* (2011) has broadly classified PD into Subtype 1 was mildly affected in all domains, Subtype 2 was predominantly characterized by severe motor complications, Subtype 3 was affected mainly on non-dopaminergic domains without prominent motor complications, while Subtype 4 was severely affected on all domains whereas this study has subclassified PD based on NMS symptoms. PD subtyping of various non-motor symptoms plays a significant role in therapeutic management in PD. This knowledge could be important for the development of tailored treatment strategies and will indeed lead to good prognosis of disease, a better quality of life and a significant reduction of burden over the caregiver (spouse).

## Conclusion

This tertiary study reveals that Non Motor symptomatology is present in 80-85% in Parkinson's Disease patients. When NMS are evaluated it is possible to subtype into following group such as Sensory Symptoms, Fatigability, Neuropsychiatric, Sleep disorders, Autonomic and Combination (visual and olfactory symptoms) which is useful in initiation and modification of therapeutics in PD.

## REFERENCES

- Aarsland D, Larsen JP, Tandberg E. and Laake K. 2000. Predictors of nursing home placement in Parkinson's Disease: A population based prospective study. *J Am Geriatr Society.*, 48:938-42.
- Barnes, T.R. 1989. A rating scale for drug-induced akathisia. *British Journal of Psychiatry*, 154,672-676.
- Barone, A Antonini and C. Colosimo, 2009. The PRIAMO study: A multicenter assessment of non motor symptoms and their impact on quality of life in Parkinson's Disease. *Movement Disorders*, 24(11):1641-49.
- Behari, M. 1999. Treatment of Parkinson's Disease: fighting the surging enemy. *Neurol India.*, 47:259-62.
- Birgit Hogl, Klaus Seppi, Elisabeth Brandauer, Susanne Glatzl, Birgit Frauscher, 2003. Ulrike Niedermuller, Gregor Wenning, Werner Poewe. Increased Daytime Sleepiness in Parkinson's Disease: A Questionnaire Survey. *Movement Disorders*, Vol.18, No.3.
- Chang Soo Kim, Young Hee Sung, Min Ju Kang and Kee Hyung Park, 2016. Rapid Eye movement sleep behaviour disorder in Parkinson's Disease: A preliminary study. *J Movement Disorder*, 2.
- Chaudhuri, K.R., Healy D.G. And Schapira A.H.V. 2006. Non-motor symptoms of Parkinson's Disease: Diagnosis and management. *Lancet Neurol.*, 5:235-45.
- Chaudhuri, K.R., Pal, S. and Di Marco *et al.*, A. 2002. "The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal ability in Parkinson's disease," *Journal of Neurology Neurosurgery and Psychiatry*, vol.73, no.6, pp.629-635.
- Chaudhuri, K.R., Yates, L. and Martinez-Martin, P. 2005. The non motor symptom complex of Parkinson's Disease: Time for a comprehensive assessment. *Curr Neurol Neurosci Rep.*, 5:275-83.
- Christopher G, Goetz, Stanley Fahn, Pablo, Martinez- Martin, Werner Poewe and Cristina Sampaio *et al.* 2007. Movement disorder society sponsored revision of the Unified Parkinson's Disease rating scale (MD-UPDRS) process, format and clinimetric testing plan. *Mov Disord.*, 22(1):41-47.
- De Lau, L.M. and Breteler, M.M. 2006. Epidemiology of Parkinson's Disease. *Lancet Neurol.*, 5:525-35.
- Deepti Vibha, Garima Shukla, Vinay Goyal, Sumit Singh, Achal Kumar Srivastava and Madhuri Behari, 2013. RBD in Parkinson's disease: A clinical case control study from North India. 2011 Elsevier B. V. *Neurology*, volume 80, No.7, Supplement P 06.096
- Diederich, N.J., R. Raman, S. Leurgans and C.G. Goetz, 2002. Progressive worsening of spatial and chromatic processing deficits in Parkinson's Disease. *Archives of Neurology*, 59(8):1249-1252.
- Doty, R.L. Studies of olfactory dysfunction in major neurological disorders, smell and taste center, University of Pennsylvania Medical Center, 3400 Spruce street, Philadelphia, PA 19104, USA. *Advances in the Biosciences*, 93:593-602.
- Folstein, M.F., Folstein, S.E. and McHugh, P.R. 1975. "Mini Mental Status". A practical method of grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12(3):189-98.
- Gelb, D.J., Oliver, E. and Gilman, S. 1999. Diagnostic criteria for Parkinson's disease. *Arch Neurol.*, 56(1):33-39.
- Goetz, C.G., Poewe, W. and Rascol, O. 2004. Movement disorder society task force report on the Hoehn and Yahr staging scale: Status and recommendations. *Mov Disord.*, 19:1020-80.
- Grosset, D., Taurah, L. and Burnet, D.J. 2007. "A multicentre longitudinal observational study of changes in self reported health status in people with Parkinson's disease left untreated at diagnosis," *Journal of Neurology, Neurosurgery and Psychiatry*, vol.78, no.5, pp.465-469.

- Hely, M.A., Morris, J.G.L., Reid, W.G.J. and Trafficante, R. 2005. Syndey multicenter study of Parkinson's Disease: Non L-Dopa responsive problems dominate at 15 years. *Movement Disorder.*, 20: 190-9.
- Hu, M., Cooper, J., Beamish, R., Jones, E. and Butterworth, R. 2011. Catterall L *et al.* How well do we recognise non motor symptoms in a British Parkinson's Disease population? *J Neurol.*, 258(8):5972-6.
- Johns, M. W. 1991. " A new method for measuring day time sleepiness: the Epworth sleep in essscale" *Sleep*, 14 (6): 540-5.
- Kumar, S., Bhatia, M. and Behari, M. 2002. Sleep disorders in Parkinson's disease. *Movement Disorder*, 17:755-81.
- Larsen, J.P., Dupout P.E. and Tandberg, E. 1994. The clinical diagnosis of Parkinson's disease: proposal of diagnostic sub-group classified at different levels of confidence. *Arch Neurol Scand.*, 84: 242-251.
- Matsui, H. and F. Udaka, 2006. A Tamura. Impaired visual acuity as a risk factor for visual hallucinations in Parkinson's Disease. *Journal of Geriatric Psychiatry and Neurology.*, 19(1):36-40
- Matthew, A. Brodsky, James Godbold, Tom Roth, C. 2003. Warren Olanow. Sleepiness in Parkinson's Disease: A Controlled Study. *Movement Disorders*, Vol.18, No.6, pp. 668-672.
- Mitra, K., Gangopadhyaya, P.K., Das, S.K. 2003. Parkinsonism plus syndromes- A review. *Neurology India*, 5:183-8.
- O'Sullivan, SS., Williams, DR., Gallagher, A., Massey, LA., Silveria-Moriyama, L. and Lees. J. 2008. Non motor symptoms as presenting complaints in Parkinson's Disease: A clinicopathological study. *Movement Disorders.*, 23(1):101-106
- Parkinson J. 1817. An Essay on the shaking palsy. London Sherwood. Neely and Jones.
- Poewe W. 2007. Non motor symptoms in Parkinson's disease. In: Jankovic J, Tolosa E eds. *Parkinson's disease and movement disorders* 5<sup>th</sup> ed. Philadelphia: Lippincott Williams and Wilkins, 67-76.
- Przedborski S. 2007. Etiology and pathogenesis of Parkinson's Disease. In: Jankovic J, Tolosa E, eds. *Parkinson's Disease and Movement Disorders* 5<sup>th</sup> ed. Philadelphia: Lippincott Williams and Wilkins, 77-92.
- Sanju P. Joy, Sanjib Sinha, Pramod Kumar Pal, Samhita Panda, Mariamma Philip and Arun B. Taly, 2014. Alterations in Polysomnographic (PSG) profile in drug-naïve Parkinson's disease. *Annals of Indian Academy of Neurology*, July-September, Vol 17, Issue 3.
- Schrag, A., Jahanshahi, M. and Quinn, N. 2000. What contributes to quality of life in patients with Parkinson's Disease? *J Neurol Neurosurg Psychiatry*, 69:308-12.
- Sebastian Paus, Hans Michael Brecht, Jurgen Koster, Gert Seeger, Thomas Klockgether, Ullrich Wullner. Sleep Attacks, Daytime Sleepiness, and Dopamine Agonists in Parkinson's Disease. *Movement Disorders* Vol. 18, No. 6, 2003, pp. 659-667.
- Shulman, L.M., R.L. Taback, J. Bean and W.J. Weiner, 2001. Comorbidity of the non motor symptoms of Parkinson's Disease. *Movement Disorders*, 16 (3): 507-10.
- Stephanie, M., Van Rooden, Fabrice Colas, Pablo Martinez-Martin, Martine Visser and Dagmar Veerbaan *et al.* 2011. Clinical subtypes of Parkinson's disease. *Movement disorders*, 26(1):
- Stiasny-Kolster, K., Mayer, G., Schäfer, S., *et al.* 2007. The REM sleep behavior disorder screening questionnaire—a new diagnostic instrument. *Mov Disord.*, 22:2386-93
- Tandberg, E., Larsen, J.P. and Karlsen, K. 1998. A community based study of sleep disorders in patients with Parkinson's disease. *Movement disorders*, 13:895-9.
- Tanya Simuni, Chelsea Caspell- Garcia, Christopher Coffey, Lama M. Chahine, Shirley Lasch, Wolfgang H. Oertel, Geert Mayer, Birgit Hogg, Ron Postuma, Aleksandar Videnovic, Amy Willis Amara and Ken Marek, 2015. Correlates of Excessive Daytime Sleepiness in De Novo Parkinson's Disease: A Case Control Study. *Movement Disorders*, Vol. 30, No.10.
- Tolosa, E., Gaig, C., Santamaria, J. and Compta. Y. 2009. Diagnosis and the premotor phase of Parkinson's Disease *Neurology.*, 72(7):S12-S20.
- Witjas, T., Kaphan, E. and Azulay, JP. 2002. Non motor fluctuations in Parkinson's Disease. Frequent and Disabling. *Neurology.*, 59(3):408-413.

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