EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 8
661-669
Year: 2020

NEUROPSYCHIATRIC DISTURBANCES IN PATIENTS WITH IDIOPATHIC PARKINSON'S DISEASE IN A TERTIARY CARE TEACHING HOSPITAL

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Article Received on 21/06/2020 **Article Revised on 11/07/2020** **Article Accepted on 31/07/2020**

ABSTRACT
Parkinson's disease is a progressive, disabling, neurodegenerative disease which is more common in Indian population nowadays. Patients with Parkinson's disease often present several neuropsychiatric symptoms. The objectives of the study was to find out the incidence of neuropsychiatric disorders, quality of life and medication adherence in patients with idiopathic parkinson's disease. Study was conducted in the Department of Neurology, Government Medical College Hospital, Thiruvananthapuram., Kerala, India with 85 patients. It's a Prospective cohort study with duration of six months. A written informed consent was obtained from the patient or caregiver before commencing the study. Patients were followed up for a period of 3 months. Majority of patients were in the age group 61- 70 years with a slight female predominance. Out of the 85 patients, 28 patients had neuropsychiatric symptoms. The assessment of disease severity by UPDRS and Hoehn & Yahr staging showed that the treatment has significantly improved the motor symptoms, patient's behavior, mood and activities of daily living. Anxiety and depression was not common in the study population. The quality of life domains such as mobility, activities of daily living, emotional wellbeing and overall quality of life had significant association with the neuropsychiatric symptoms. Majority of patients showed high adherence to the medications. The study was able to describe the incidence of neuropsychiatric symptoms in Idiopathic Parkinson's Disease patients and its association with other motor symptoms and quality of life. The present study emphasizes the importance of early detection of psychiatric symptoms such as depression which was present in most of the patients. Further research involving large sample size and long term follow up is essential to determine the extent to which improvement is achieved in motor functions, quality of life and cognitive function parkinsonism patients.

KEYWORDS: Depression and anxiety, Medication adherence, Motor symptoms, Neuropsychiatric disorders, Parkinson's Disease, Quality of life.

INTRODUCTION
Parkinson's disease (PD) was originally described in 1817 by James Parkinson, a British physician. The disease in which there is no known cause is known as idiopathic PD.

Parkinson's disease is a progressive, disabling, neurodegenerative disease which is more common in Indian population nowadays. Patients with Parkinson's disease often present several neuropsychiatric symptoms. As there are only few studies in the Indian literature regarding the neuropsychiatric symptoms in PD patients, the present study is undertaken. No similar study was done in the current study set up. This study is designed to look at the incidence of neuropsychiatric disturbances in patients with Parkinson's disease.

Pharmacological intervention is essential for managing the symptoms of PD. Several studies have shown that PD patients have low quality of life and medication adherence. This is especially because the symptoms of cognitive impairment and anxiety and depression are more prevalent. Improved quality of life is an indication of the effectiveness of treatment. Hence, evaluation of the quality of life is highly relevant. Poor adherence can result in wearing off of the treatment effect which can significantly increase motor dysfunction.[21] Treatment of Parkinson's disease requires medications to be taken regularly for long time. Hence, medication adherence is very important factor which modifies the drug therapy. Majority of patients are coming from rural areas and from poor socio economic background since specialized care for PD patients at low cost is available in the tertiary care centres run by the Government. Pharmacist can play a crucial role in improving medication adherence and

quality of life by providing proper counseling to patients as well as caregivers. So, the study on incidence of neuropsychiatric symptoms, quality of life, medication adherence and direct cost of treatment is relevant in the present situation.

METHODOLOGY

Objectives

- To study the incidence of neuropsychiatric disorders in patients with idiopathic parkinson's disease.
- To evaluate the quality of life in PD patients before and after treatment.
- To assess the medication adherence in PD patients.

Study setting: Tertiary care setting, Department of Neurology, Government Medical College Hospital, Thiruvananthapuram.

Study design: Prospective cohort study.

Sample size: 85 patients

Study period: Six months

Inclusion criteria

- Patients diagnosed as having idiopathic Parkinson's Disease based on the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria attending the Department of Neurology, Government Medical College Hospital, Thiruvananthapuram.
- Those who gives consent voluntarily to participate in the study.

Exclusion criteria

- Patients who have loss of vision, deafness.

Procedure: A written informed consent was obtained from the patient or caregiver before commencing the study. A cohort of patients with idiopathic PD was assessed for neuropsychiatric symptoms and their baseline scores were recorded. Patients were followed up for a period of 3 months. All patients were administered the Unified Parkinson's Disease Rating Scale (UPDRS) and were staged based on Hoehn & Yahr stages 1 to 4. Close relatives (spouse and children) of the enrolled patients or the healthy participating subjects were interviewed using the twelve subscale version of Neuro Psychiatric Inventory (NPI) to determine the incidence of neuropsychiatric symptoms. Anxiety and depression in PD patients were self rated using Hospital Anxiety and Depression Scale (HADS). Also, cognitive function was assessed using Addenbrooke's Cognitive Examination (ACE). Quality of life was evaluated using PDQ-39 questionnaire. Medication adherence was assessed using Morisky Medication- Taking Adherence Scale – 4.

RESULTS

Table 1: Distribution of the patients according to age.

AGE IN YEARS	FREQUENCY	PERCENTAGE
<30	1	1.2
31-40	3	3.5
41-50	17	20.0
51-60	23	27.1
61-70	30	35.3
>70	11	12.9
Total	85	100.0

Table 2: Distribution of patients according to gender.

GENDER	FREQUENCY	PERCENTAGE
Male	41	48.2
Female	44	51.8
Total	85	100.0

Table 3: Distribution of patients according to UPDRS scores.

DOMAINS		N	Mean	sd	t	P
Mentation, behavior and mood	Base line	81	2.8	1.9	5.248	<0.001
	Follow up	81	1.9	1.7		
Activities of daily living	Base line	81	12.5	6.1	7.023	<0.001
	Follow up	81	9.2	5.9		
Motor examination	Base line	81	26.1	12.2	8.456	<0.001
	Follow up	81	19.1	11.2		
Complications of therapy	Base line	81	4.9	1.7	3.721	<0.001
	Follow up	81	4.3	1.6		
Total UPDRS score	Base line	81	46.3	18.8	9.729	<0.001
	Follow up	81	34.6	16.8		

Table 4: Categorization of patients based on severity of disease according to Hoehn & Yahr staging.

H & Y STAGE	Baseline		Follow up	
	N	%	N	%
Stage 0	3	3.5	3	3.5
Stage 1	17	20.0	20	23.5
Stage 1.5	5	5.9	3	3.5
Stage 2	30	35.3	32	37.6
Stage 2.5	12	14.1	10	11.8
Stage 3	15	17.6	11	12.9
Stage 4	2	2.4	2	2.4
Stage 5	1	1.2	1	1.2
Lost follow up			3	3.5
Total	85	100.0	85	100.0

Table 5: Incidence of neuropsychiatric symptoms: Neuropsychiatric inventory scale.

NPI	Baseline		Follow up	
	N	%	N	%
Delusions	6	7.1	2	2.5
Hallucinations	2	2.4	3	3.8
Agitation/ Aggression	8	9.5	2	2.5
Depression/ Dysphoria	11	13.1	3	3.8
Anxiety	5	6	2	2.5
Elation/ Euphoria	0	0	0	0
Apathy/ Indifference	2	2.4	2	2.5
Disinhibition	1	1.2	1	1.3
Irritability/ Liability	7	8.3	2	2.5
Aberrant motor behavior	0	0	0	0
Night time behavior	3	3.5	1	1.2
Appetite/ eating changes	1	1.2	1	1.2

Table 6: Categorization of patients based on anxiety score of HADS.

ANXIETY	FREQUENCY	PERCENTAGE
Normal	42	49.4
Borderline abnormal	30	35.3
Abnormal	13	15.3
Total	85	100.0

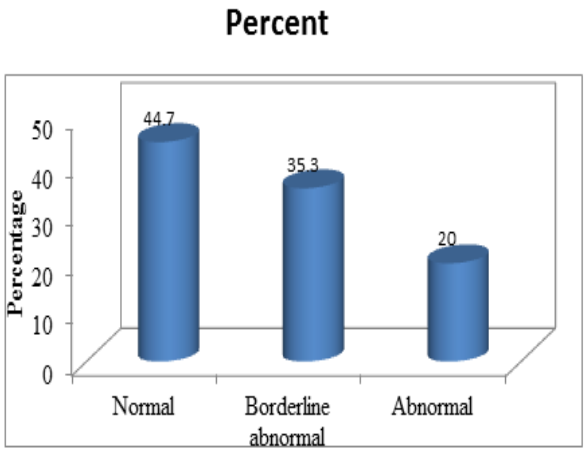

Figure 1: Categorization of patients based on depression score of HADS.

Table 7: Cognitive examination: Addenbrooke's Cognitive Examination scale.

ACE DOMAINS	N	Mean	sd	Minimum	Median	Maximum
Orientation	85	8.6	2.3	2.0	10.0	10.0
Attention	85	6.4	1.7	3.0	7.0	8.0
Memory	85	19.9	7.7	2.0	20.0	35.0
Verbal fluency	85	7.8	2.8	1.0	8.0	14.0
Language	85	21.8	4.9	7.0	23.0	28.0
Visuospatial abilities	85	1.6	1.8	0.0	1.0	5.0
ACE grand total	85	66.0	16.6	28.0	69.0	98.0

Table 8: QOL assessment using PDQ - 39 scale.

QOL DOMAINS	N	Mean	sd	Minimum	Median	Maximum
Mobility	85	43.5	17.0	20.0	42.0	80.0
ADL	85	44.4	22.8	20.0	44.0	92.0
Emotional wellbeing	85	34.6	15.2	20.0	33.3	86.7
Stigma	85	25.8	12.2	20.0	20.0	90.0
Social support	85	23.8	9.2	20.0	20.0	53.3
Cognitive impairment	85	31.3	11.8	20.0	25.0	65.0
Communication	85	27.8	12.9	20.0	20.0	73.3
Bodily discomfort	85	37.4	16.3	20.0	33.3	93.3
Grand total	85	36.2	12.0	16.4	34.9	68.7

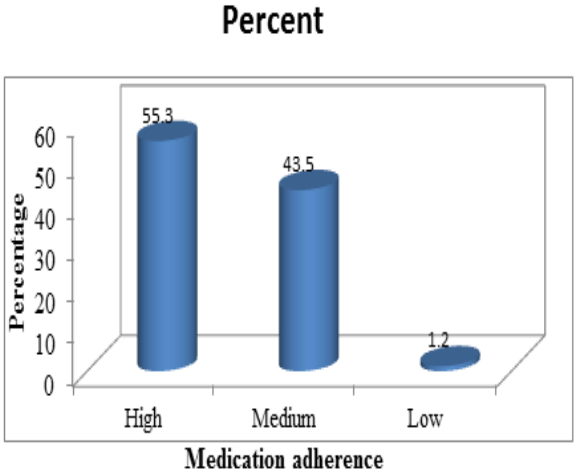

Figure 2: Categorization of patients based on medication adherence.

Table 9: Association of NPI symptoms with UPDRS.

UPDRS DOMAINS		NPI symptoms				t	p
		Present (N=28)		Absent (N= 57)			
		Mean	sd	Mean	sd		
Mentation, behavior and mood	Baseline	3.2	2.3	2.4	1.7	1.772	.080
	Follow up	2.5	2.1	1.6	1.4	2.167	.033
Activities of daily living	Baseline	15.5	6.5	10.9	5.3	3.464	.001
	Follow up	12.4	6.2	7.6	5.0	3.811	.000
Motor examination	Baseline	29.1	12.9	24.1	11.4	1.797	.076
	Follow up	23.0	12.5	17.1	10.1	2.322	.023
Complications of therapy	Baseline	4.8	1.4	5.0	1.8	0.466	.643
	Follow up	4.3	1.4	4.3	1.7	0.087	.931
Total UPDRS score	Baseline	52.5	20.2	42.4	16.9	2.422	.018
	Follow up	42.2	19.1	30.6	14.1	3.113	.003

Table 10: Association of NPI symptoms with QOL.

QOL DOMAINS	NPI symptoms				T	p
	Present (N=28)		Absent (N= 57)			
	Mean	sd	Mean	Sd		
Mobility	52.1	16.9	39.2	15.5	3.517	.001
Activities of daily living	52.0	23.1	40.7	21.8	2.200	.031
Emotional wellbeing	40.0	15.2	32.0	14.6	2.342	.022
Stigma	25.9	7.2	25.8	14.0	.037	.971
Social support	23.8	9.7	23.9	9.1	.023	.981
Cognitive impairment	34.3	10.2	29.8	12.3	1.662	.100
Communication	27.1	10.3	28.2	14.1	.348	.729
Bodily discomfort	38.3	12.9	37.0	17.8	.364	.717
Grand total	40.7	10.8	34.0	12.0	2.499	.014

Table 11: Association of NPI symptoms with medication adherence.

		NPI symptoms				Total		χ^2	df	p
		Present (N=28)		Absent (N= 57)						
		N	%	N	%	N	%			
Adherence	High	13	27.7	34	72.3	47	100.0	1.328	2	0.249
	Medium/Low	15	39.5	23	60.5	38	100.0			

Table 12: Association of NPI symptoms with ACE scale domains.

ACE DOMAINS	NPI symptoms				T	P
	Present (N=28)		Absent (N= 57)			
	Mean	sd	Mean	Sd		
Attention	6.5	1.7	6.3	1.7	0.334	.739
Orientation	8.8	2.1	8.5	2.4	0.624	.534
Memory	19.2	7.6	20.2	7.7	0.581	.563
Verbal fluency	7.4	2.4	7.9	3.1	0.761	.449
Language	20.7	5.0	22.3	4.8	1.431	.156
Visuospatial abilities	1.3	1.7	1.7	1.8	0.957	.342
ACE total score	63.9	16.7	67.0	16.7	0.799	.427

DISCUSSION

Sociodemographic background

Out of 85 patients, majority (35.3%) were in the age group of 61- 70 years. 27.1% were in the age group of 51- 60. This indicates an increased incidence of disease after 60 years and is supported by the studies done by J. Ray *et al.*[19] Majority of patients in the study group were females (51.8%) and 48.2% were males. This indicates a slight more prevalence of IPD in females. The result was similar to the findings of the studies conducted by D. Aarsland *et al.*[29] Among the 85 IPD patients under study, majority (91.8%) were non vegetarians and only 8.2% were vegetarians.

In the study group, majority of patients belong to APL category (62.4%) and 37.6% of patients belong to BPL category. There was a slight prevalence of IPD among high income groups. In the study population, majority of patients were residing in rural areas (59%) and only 26% of patients were from urban areas. Out of the 85 patients included in the study, majority (85.9%) were unemployed and only 14.1% were employed.

Among the study population, only 1.2% had family history of IPD and majority (98.8%) had no family history of the disease in their first degree relatives. The result suggests that there is no relationship between family history and the disease. Majority of patients in the study population were having 8 - 10 years of education (38.8%) and only 4.7% of patients were illiterate. More than 70% of patients had above 5 years of education. This result reflects the high literacy rate of people in Kerala.

Drugs used in treatment: In the study population, majority of patients (76.5%) were using Levodopa + Carbidopa combination as their medication. Other medications prescribed for the study group were Amantadine (33%), Pramipexole (28.2%), Trihexyphenidyl (28.2%) and Rasagiline (2.4%). This indicates that among the Anti- parkinsonian agents Levodopa + Carbidopa combination is the most prescribed.

Distribution of patients according to updrs scores: The mean scores of all the four domains were decreased at follow up: mentation, behavior and mood (2.8 to 1.9), ADL (12.5 to 9.2), motor examination (26.1 to 19.1) and complications of therapy (4.9 to 4.3). Total UPDRS mean score is also decreased from 46.3 to 34.6. All these

differences are statistically significant with p value <0.001. This represents a significant symptom improvement in patients with parkinsonism under study. The result was supported by the studies conducted by Davidson MB *et al*.[51]

Severity of disease according to hoehn & yahr staging: According to modified Hoehn & Yahr staging of parkinson' s disease which is a rating tool to assess the disease severity, stage 2 was most frequent among the subjects under this study at both baseline (36.5%) and follow up (37.6%). Stage 1 was also more frequent at baseline (20%) and at follow up (23.5%). This result was supported by the findings of S. Bharath *et al*[52] who reported that majority of patients were H & Y stage 1 and stage 2.

Neuropsychiatric inventory scale: In the present study, out of the 85 patients included, a total 28 patients had neuropsychiatric symptoms present during the study period. Of the 12 items of NPI, depression is the major symptom present in the patients (16.9%), agitation/ aggression in 12% and irritability/ liability in 10.8% of patients. All the symptom scores were decreased at follow up except for hallucinations, apathy and disinhibition where a slight increase in incidence was seen. The results suggests some improvement in the incidence of NP symptoms after treatment. Elation/euphoria and aberrant motor behavior were least common symptoms in the study population. This result correlates with the findings of the study conducted by Dag Aarsland et al.[32] Depression was the major neuropsychiatric symptom in IPD patients which almost agree with the findings of Richard IH *et al*,[53] Kulisevsky *et al*[27] and Stakstein SE *et al.*[54]

Npi - caregiver distress: Caregiver distress scores for all the 10 domains of NPI questionnaire was noted at both baseline and follow up. The total mean score of caregiver distress at baseline was 0.5 and at follow up was 0.2. In this study, majority of parkinson's disease caregivers had no distress.

Patients based on anxiety score of hads: In the present study population, only 15.3% of patients were abnormal or anxious, 35.3% were borderline abnormal and majority (49.4%) were normal having no anxiety symptoms.

Patients based on depression score of hads: Among the study population, 20% of patients had depression, 35.3% were borderline abnormal and majority of patients were normal or not depressed (44.7%). This result was not supported by the study conducted by Kulisevsky *et al*.[27]

Addenbrooke's cognitive examination scale: In the study population, cognitive function assessment was done using ACE scale. The highest mean score was found for the domains language (21.8) and memory (19.9). In the present study education has significant correlation with cognitive function.

Qol assessment using pdq - 39 scale: In the present study, PDQ - 39 questionnaire is used to evaluate the QOL. The highest mean score was found for the domains ADL (44.4) and mobility (43.5). This indicates that the QOL is not much affected by the disease in all domains. Overall quality of life mean score was 36.2 which means that no significant deterioration in the QOL was found in the study population and most of the patients have good quality of life.

Based on medication adherence: In the present study, patients were categorized into high, medium and low adherence groups according to morisky medication adherence scale - 4. Majority of patients were highly adherent to the antiparkinsonian medication (55.3%) and only 1.2% were non adherent. This indicates the high awareness of people about the importance of taking medications correctly. Also, oral medication improves therapy response or adherence in PD patients. This result was similar to the findings of the study conducted by Grosset D *et al*.[43]

Association of incidence of npi symptoms with updrs In the present study population, the mean score of UPDRS I in patients with NP symptoms at baseline was 3.2 ± 2.3 and in patients without symptoms it was 2.4 ± 1.7. At follow up the mean score in both groups was 2.5 ± 2.1 and 1.6 ± 1.4 respectively. In the 28 patients with neuropsychiatric symptoms, the mean scores of UPDRS I, II, III and total UPDRS scores showed a significant increase as compared to the remaining 57 patients without symptoms. No significant change was seen in the UPDRS IV domain. This indicates that UPDRS score influences the incidence of NP symptoms. This result is not supported by the findings of Goetz CG *et al*.[30]

Association of incidence of npi symptoms with hoehn & yahr staging: In the present study, the mean H & Y stage in patients with NP symptoms at both baseline and follow up was higher than that in patients without NP symptoms. This suggests the increased disease severity in patients with NP symptoms. This result was supported by the findings of the study conducted by Antonini. A *et al*.[25]

Npi - caregiver distress: In the study group, at baseline, caregiver distress was present in 24 patients and at follow up only 15 patients had distress. The difference was statistically significant and p value was 0.035. In other words, of the 28 patients with NP symptoms, 24 had caregiver distress present and 4 had no distress. Of the 57 patients without NP symptoms no caregiver distress was considered. The results suggested that as the NP symptom improved by treatment, caregiver distress will become absent. Majority of patients in the study population had no associated caregiver distress.

Association of incidence of npi symptoms with had scale: In the study population, means score of anxiety in patients with NP symptoms was 8.4 ± 2.3 and in patients without NP symptoms it was 7.2 ± 2.9. The difference was not statistically significant. Depression also has no significant association with incidence of NP symptoms.

Association of incidence of npi symptoms in patients with anxiety score using hads: In the study population, of the 13 abnormal patients, 30.8% had NP symptoms and in the 30 borderline abnormal group patients, 46.7% had NP symptoms. There was no statistically significant relation between incidence of NP symptoms and anxiety.

Association of incidence of npi symptoms in patients with depression score using hads: In the present study, of the 17 abnormal or depressed patients, 35.3% had NP symptoms In the 30 patients with borderline abnormal level of depression, 33.3% had NP symptoms. This indicates a high incidence of depression in patient with NP symptoms. The scores of depression in the study group ranges from 8 to 11 or 11 and above. This result correlates with the findings of the study conducted by Kulisevsky *et al*.[27]

Association of incidence of npi symptoms with ace scale domains: Among the 28 patients with NP symptoms**,** the highest mean score of ACE was 63.9 ± 16.7 and in patients without NP symptoms it was 67.0 ± 16.7. Highest mean score was found for the domains, language (20.7 ± 5.0) and memory (19.2 ± 7.6). But there was no statistically significant association between cognitive function and NP symptoms. The result was not supported by the studies done by Morgante. L *et al*.[23]

Association of incidence of npi symptoms with qol Among the 28 patients with NP symptoms the mean score of mobility was 52.1 ± 16.9 and in patients without NP symptoms was 39.2 ± 15.5. The result was statistically significant (p= 0.001). The overall QOL score also had a significant decrease in patients without NP symptoms as compared to patients with NP symptoms (p = 0.014). No significant difference was found on cognitive impairment domain. The above result suggested that the incidence of NP symptoms has a major influence on the QOL in IPD patients. The results correlated with the findings of the studies conducted by A. Shrag *et al*.[33], Kristine. KH *et al*.[36] and Heluani AS *et al*.[40]

Summary

The study results are summarized below.

The socio demographic factors identified in the present study revealed that

- Majority of patients were in the age group 61- 70 years.
- The disease has a slight female predominance.
- Most of the study population were non vegetarians, belongs to APL category, residing in rural areas.
- Majority of patients were unemployed, have 8 to 10 years of education and have no family history of the disease.
- Levodopa + Carbidopa combination is the most commonly prescribed antiparkinsonian medication.

The clinical background of the study revealed that:

The incidence of neuropsychiatric symptoms were measured by using Neuro Psychiatric Inventory scale. Out of the 85 patients, 28 patients had neuropsychiatric symptoms. Depression is the major symptom present in patients (13.1%) and agitation/ aggression and irritability was also present. There was slight improvement in the incidence of neuropsychiatric symptoms after treatment. Elation/ euphoria and aberrant motor behavior was the least common symptoms present in patients and the other 10 items of NPI were present in some of the patients singly or as more than one. Majority of the parkinson's disease caregivers have no distress by the patient. There is significant relationship between incidence of neuropsychiatric symptoms and distress in caregivers.

The assessment of disease severity by UPDRS and Hoehn & Yahr staging showed that the treatment has significantly improved the motor symptoms, patient's behavior, mood and activities of daily living. There is significant association between UPDRS scores and incidence of neuropsychiatric symptoms in patients.

Anxiety and depression was not common in the study population. Only least majority of patients had the symptoms present. Also cognitive function was not impaired much by the disease. All these factors had no significant association with incidence of neuropsychiatric symptoms.

The quality of life domains such as mobility, activities of daily living, emotional wellbeing and overall quality of life had significant association with the neuropsychiatric symptoms. All the above domains had a significant deterioration in the study group with neuropsychiatric symptoms as compared to patients in whom the symptoms are absent. Majority of the study population had good quality of life. The may be due to better treatment and caregiver support.

Majority of patients showed high adherence to the medications and there was no significant association existing between incidence of neuropsychiatric symptoms and medication adherence.

CONCLUSION

The study was able to describe the incidence of neuropsychiatric symptoms in Idiopathic Parkinson's Disease patients and its association with other motor symptoms and quality of life. Only some of the patients with parkinson's disease had neuropsychiatric symptoms present. The present study emphasizes the importance of early detection of psychiatric symptoms such as depression which was present in most of the patients. It

also suggested that neuropsychiatric symptoms had no significant association with disease severity and cognitive function. Both medication and counseling therapies and caregiver support is useful. Further research involving large sample size and long term follow up is essential to determine the extent to which improvement is achieved in motor functions, quality of life and cognitive function parkinsonism patients.

ACKNOWLEDGEMENTS

I express my sincere, deep sense of gratitude and immense respect to my esteemed Guide, **Sri. Jayakrishnan S.S** and Co-guide **Dr. Thomas Iype,** for their great inspirations, valuable suggestions, never diminishing encouragement and excellent guidance throughout the study.

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