



PREVALENCE AND CORRELATION WITH CLINICO RADIOLOGICAL FEATURES OF PARKINSON'S DISEASE WITH AUTONOMIC DYSFUNCTION

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Abstract

Introduction: Autonomic dysfunction occurs not only in advanced PD but also early in its course. Transcranial ultrasound can pick up SN abnormalities very early in the disease. There are no Indian studies which correlated autonomic dysfunction with TCUS findings. **Objectives:** This study aims to study prevalence of autonomic dysfunction, to correlate with clinico-imageological features and to assess the impact of autonomic dysfunction on quality of life. **Materials and methods:** This is a Retrospective and Prospective study, with 45 PD patients taken from Movement clinic, NIMS, Hyderabad from Jan 2016-June 2017. PD diagnosis based on UKPD society Brain Bank Criteria, For motor evaluation –1)H&Y staging 2)UPDRSIII on off staging, Questionnaires used were 1.SCOPA–AUT, 2.PDQ 39, 3.MOCA&Lab Tests: 1. Autonomic Function Tests, 2. Transcranial ultrasound. **Results:** Out of 45 patients males were 34 and females were 11. The mean UPDRS III Off Score and On Score were 47.7 ± 14.6 and 15.4 ± 7.7 respectively. The mean H and Y score was 2.1. The PDQ-39SS and SCOPA- AUTSS were 57.6 ± 34.6 (0-120) and 6.33 ± 5.4 (0-23) respectively. The Parasympathetic and Sympathetic dysfunction found in 53% (N-24) and 31% (N-19) respectively. 24(53%) had tremor and 21(47%) had rigidity predominance. The parasympathetic and sympathetic dysfunction on AFT were more in tremor patients compared to rigidity patients (p value-0.001 for parasympathetic and 0.003 for sympathetic dysfunction. Significant Laterality index was found in 38 (84.44%). **Conclusions:** Most common self-reported autonomic symptoms were constipation and postural dizziness. AFT showed significant autonomic dysfunction even in those who had no autonomic symptoms. Based on our and previous studies we recommend objective autonomic function evaluation in every patient of IPD. SN hyperintensity didn't correlated with autonomic dysfunction. PDQ39sum Score was higher in those with autonomic dysfunction affecting quality of life.

Key Words: Parkinson's disease, autonomic dysfunction, clinic-imageological features

I. Introduction

Parkinson's disease (PD) is a progressive debilitating neurodegenerative disease that affects dopaminergic neurotransmission, resulting predominantly in bradykinesia, rest tremor, and rigidity.

⁽¹⁾ Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor

dysfunction (parkinsonism) and several non-motor features.

Autonomic dysfunction can occur even in the early stages of PD, often preceding the onset of the classic motor symptoms. Like other non-motor symptoms, autonomic dysfunction seriously limits physical activities, decrease quality of life, and impose a major financial burden. ⁽²⁾

Autonomic and cognitive impairments do not respond to dopamine supplement and the frequency of non-motor symptoms invariably increases with PD progression. ⁽³⁾

In 1995, Georg Becker and his group described for the first time a disease-specific sonographic finding in Parkinson disease (PD): hyperechogenicity of the substantia nigra (SN). ⁽⁴⁾ Trans cranial ultrasound (TCS) has become a reliable and valuable tool for the diagnosis and differential diagnosis of PD and other movement

disorders. Because TCS is broadly available, quick to perform in moving patients, and inexpensive, it is worth considering as a supplementary diagnostic neuroimaging tool in general practice.

The purposes of this study were to evaluate the frequency and nature of autonomic dysfunction according to disease stage and to determine the relationship between autonomic function and clinic-imageological findings and also the effect on quality of life in Indian subgroup PD patients.

II. Aims And Objectives:

1. To study the prevalence of autonomic dysfunction in a cohort of Indian PD patients.
2. To correlate the clinico-imageological features in PD patients.
3. To assess the impact of autonomic dysfunction on the quality of life (QOL) of PD patients.

III. Material & Methods

This is a retrospective and prospective cross sectional observational study using a direct, structured interview of PD patients by movement disorder specialist. This study was conducted in Dept of Neurology, NIMS for duration of 1 ½ year from Jan 2016 to Jun 2017. The study include patients, who were diagnosed with PD, based on UKPD society Brain Bank Criteria (Hughes). All Patients attending the neurology opd/ipd who were eligible were enrolled in the study. Socio-demographic characteristics, clinical features, past history, relevant medical history and treatment history were collected and verified with the medical records. Impressions from MRI brain imaging were recorded. Current medications and their doses were recorded. The UPDRS staging was done by the movement disorder specialist in the clinic visit. Interview was conducted by using SCOPA – AUT Questionnaire which consists of 26 relevant questions related to autonomic disturbance of PD patients. The total score was assessed with grading.

Autonomic functional test was done in ENMG lab, Department of neurology under supervision of the investigator. Transcranial ultrasound, a non invasive procedure was done to all patients in Department of Radiology, NIMS, Hyderabad by an experienced radiologist in this field. PDQ-39 questionnaire was used to get the information about quality of life among PD patients. The purpose of the study was explained to the patients and a written informed consent will be taken. All interviews were conducted in the drugon state to minimize patient discomfort. The key relative was also interviewed for corroborating the details given by the patient. The differences and inconsistencies in the version and doubts of both patients and family were addressed and consistency achieved, a minimum of 60 patients were enrolled.

Study design –Retrospective and Prospective study.

Subjects & Study period – Recruited from patients diagnosed as having IPD in

Movement clinic, Neurology dept., NIMS , Hyderabad for duration of 1 1/2 year from Jan 2016 to June 2017. Clinical and Demographic profile: PD diagnosis based on UKPD society Brain Bank Criteria,

For motor evaluation –

- 1) H&Y staging 2) UPDRS III on off staging, Questionnaires - 1. SCOPA–AUT for Autonomic symptoms,
2. PDQ 39 (Quality of life) ,
3. MOCA

Lab Tests: 1. Autonomic Function Tests and 2. Transcranial ultrasound Other tests: HbA 1c and US abdomen(to evaluate prostate)

The purpose of the study was explained and a written informed consent was taken. SCOPA-AUT Questionnaire:

The self-reported SCOPA-AUT consists of 25 items assessing the following regions: gastrointestinal (7), urinary (6), cardiovascular (3), thermoregulatory (4), pupillomotor (1), and sexual (2 items for men and 2 items for women) dysfunction.

The Parkinson's Disease Questionnaire (PDQ-39)

The PDQ-39 was developed on the basis of interviews with Parkinson's disease patients and a number of large- scale surveys , consists of 8 dimensions (Mobility, Activities of daily living, Emotional well-being, Stigma, Social support ,Cognitions ,Communication, Bodily discomfort) and 39 questions.

The resulting multi-dimensional measure proved to have good internal and test-retest reliability, as well as good face and construct validity Such profile measures can be of use in gaining a picture of the impact of the disease in specific areas of functioning and well-being. (annexure)

In this study the sum scores were calculated individually in each patient and then correlated with AFT and TCS findings.

Tests of Autonomic Dysfunction:

Tests of parasympathetic dysfunction:

Heart rate (HR) response to deep breathing -E:I Ratio> 1.2

HR response to standing (30:15 ratio)- Normal > 1.04 Valsalva ratio- Normal > 1.4

Tests of sympathetic dysfunction

BP on standing : at rest , standing 1 min and at 3 min Sympathetic skin response test : present or absent

The cut off values for individual tests of autonomic function were taken as per standard reference and as per lab controlled values.

Transcranial Ultrasound(TCUS):

TCS was performed according to a standardized protocol using a e SOATE my lab Seven ultrasound machine, equipped with a 2.5- 4 Mhz transducer.

The examination procedure was strictly performed according to the consensus criteria (Berg et al., 2006; Walter et al., 2007a).

SN areas of echogenicity above the 75th percentile of the normal population are classified as “moderately hyperechogenic”(0.21cm² – 0.25 cm²) ,SN areas of echogenicity above the 90th percentile are classified as “markedly hyperechogenic” (>0.25 cm²). In the current study we have taken >0.2 cm² volume of SN as significant value to correlate with features of Parkinson's disease.

Volumes of ≤0.2 cm² was considered normal.

In the current study we have taken >0.2 cm² volume of SN as significant value to correlate with features of Parkinson's disease

Laterality of symptoms is a key feature of iPD. SN hyper echogenicity can usually be found bilaterally in iPD, although usually more pronounced contralaterally to the more affected side.(42) Marked laterality as measured by the laterality index (larger SN/smaller SN >1.15).

In this study which initially recruited 101 patients had difficulty in assessing SN because of poor temporal acoustic bone window, allowing only partial or even no assessment of brainstem structures in some patients.

Ultimately 45 patients were studied in all aspects sonologically by an experienced Neuroradiologist. Statistical analysis:

Statistical analysis was done by using SPSS trail version 16 & MS excel 2007. Quantitative variables were expressed as Mean ± SD & qualitative variables were expressed as frequencies & in percentages. Student t & ANOVA tests were used for comparison, Chi square test used for examining the categorical data. For all statistical analysis p<0.05 was considered as statistically significant.

IV. Results:

Clinical and Demographic data: A total of 101 patients were taken in to study out of which final 45 patients completed the study and 56 were excluded due to various reasons. Out of 45 patients males were 34 and females were 11. The mean age of PD patient was 59.95 ± 11.3 , age of onset was 54.62 ± 11 , the mean duration of disease and duration of LD treatment when patient was included in study were 5.33 ± 2.9 and 4.3 ± 2.5 respectively. The mean UPDRS III Off Score and On Score were 47.7 ± 14.6 and 15.4 ± 7.7 respectively. The mean H and Y score was 2.1. The PDQ-39 Sum Score and SCOPA-AUT Sum Score were 57.6 ± 34.6 (0-120) and 6.33 ± 5.4 (0-23) respectively.

Autonomic Function Test Results: In autonomic function tests performed the Parasympathetic dysfunction was found in 53% (N-24) patients and the overall Sympathetic dysfunction was found in 31% (N- 19) patients.

SCOPA –AUT Questionnaire – Symptoms and Percentage Data: Frequency distribution of autonomic symptoms and their percentages in PD patients as evaluated by SCOPA –AUT Questionnaire showed that the frequently presented autonomic symptom were constipation (53.49%), had to pass urine at night (53.49%), light headed on standing for a while (60.47%).

Table No 1: SCOPA Scores and H&Y Stages Correlation

Variables H&Y stages Number (45)	I (23)	II (9)	III–V (15)	p Value
SCOPA-AUT-Total Score	7.86 ± 6.0	9.9 ± 4.7	15.4 ± 8.0	<0.001
GI	1.5	3.0	5.5	<0.001
GU	4.7	5.1	6.9	0.032
CV	1.3	1.2	2.5	0.118
TH	0	0.6	0.3	0.256

GI – Gastrointestinal, GU – Genitourinary, CV – Cardiovascular, TH –Thermoregulatory SCOPA Scores and H&Y Stages Correlation:

The mean SCOPA-AUT total scores were 7.86 ± 6.0 in stage I of H&Y PD patients (N-23), 9.9 ± 4.7 in stage II of H&Y PD patients (N-9), 15.4 ± 8.0 in stage III–V of H & Y PD patients (N-15). SCOPA-AUT GI and GU scores as well as SCOPA AUT Total score were significantly correlated with H & Y stages.

Frequency Distribution of SCOPA sum score in PD patients (N- 45):

Out of 45 patients 12(27%) had SCOPA-AUT sum score of 0, 18(40%) had a score of 1-5, 8(18%) had score of 6-10, 6(13%) had score of 11-15, 1(2%) had score of 16-25.

SCOPA Sum Scores – Relation with AFT:

In patients with SCOPA-AUT sum score 0-2, parasympathetic dysfunction present in 9, sympathetic dysfunction present in 7. Similarly, of SCOPA-AUT sum score 3-5, 6 and 5 had parasympathetic and sympathetic dysfunction respectively.

Of patients with SCOPA-AUT sum score 6-10, 4 and 2 had parasympathetic and sympathetic dysfunction respectively. Similarly, of SCOPA-AUT sum score 11-30, 5 and 5 had parasympathetic and sympathetic dysfunction respectively.

Table No 2: SCOPA Sum Scores – Relation with AFT

SCOPA Sum Score	Parasympathetic Dysfunction	
	Present (N)	Absent (N)
SCOPA 0 TO 2	9(20%)	3(7%)
SCOPA 3 TO 5	6(13%)	6(13%)
SCOPA 6 TO 10	4(9%)	7(16%)
SCOPA 11 TO 30	5(11%)	5(11%)
Total	24(53%)	21(47%)

The patients who had even less total SCOPA-AUT score means no or less symptoms are found to have abnormal autonomic functional test results which strengthen the importance of AFT to be

done in every patient of PD. Predominant Motor symptom - frequency distribution: Out of 45 patients 24(53%) had tremor and 21(47%) had rigidity predominance.

Tremor vs Rigidity comparison: The mean sum scores of PDQ 39(Tremor -74.333, Rigidity- 38.476) and SCOPAAUT (tremor- 8.66, rigidity -3.66) were higher in tremor predominant patients compared to rigidity predominant patients with significant p value of 0.001.

The overall parasympathetic dysfunction and sympathetic dysfunction picked up on results of AFT were more in tremor predominant patients compared to rigidity predominant PD patients with significant p value of 0.001 in respect to parasympathetic and 0.003 with sympathetic dysfunction respectively. Frequency Distribution of PDQ 39 sum score in PD patients (N- 45): Out of 45 patients 1(2%) patient had PDQ 39 sum score of 0, 14(31%) patients had score of 1-20, 6(13%) patients had score of 21-40, 3(7%) patients had score of 41-60, 11(24%) patients had score of 61-80, 8(18%) patients had score of 81-100, 2(5%) patients had score of 101-120.

Out of 45 patients, parasympathetic dysfunction found in 24 patients and sympathetic dysfunction found in 19 patients. In patients with parasympathetic dysfunction, 3 patients had PDQ sum score between 0-25, 2 had PDQSS 26-59, 10 had PDQSS 60-90 and 9 had PDQ >90. Likewise, in patients with sympathetic dysfunction, 2 had PDQSS of 0-25, 8 had PDQSS between 60 - 90 and 9 patients had PDQSS >90.

Patients without autonomic dysfunction had lower scores of PDQ39 sum scores and patients with autonomic dysfunction had higher PDQ39 sum scores.

PDQ sum score subgrouping was done (0-25, 26-59, 60-90 and >90) and subgroup 0- 25. Comparison with other PDQ subgroups was done using t-test on analysis.

There is significant increase in mean sum of SCOPA score (2.11(PDQ 0-25 Vs PDQ 26-59), 5.31 (PDQ 0-25 Vs PDQ 60-90), 8.74(PDQ 0-25 Vs PDQ >90)).it is also correlated with parasympathetic and sympathetic dysfunction but there is no correlation with volume of SN findings of TCUS. Here Correlation matrix is used to test for the significance of relationships between two variables i.e., AFT and TCUS. We found no significant relationship between these two variables.

Volume of right Substantia Nigra > 0.2 cm² is seen in 6 out of 45 patients(13.33 %). Volume of left Substantia Nigra > 0.2 cm² is seen in 16 out of 45 patients (35.55%). Bilateral enlargement of Substantia Nigra > 0.2 cm² is seen in 3 (6.66%). Volumes of SN are moderately enlarged in more than 93% of PD patients. Normal volumes but with interside variability in volumes and hyperechoic nature is seen in 3 (6%). Laterality index (larger SN/smaller SN >1.15) were 38 out of 45 (84.44%).

Table No 3: Volume of right SN Hyper echogenecity

Volume of right SN Hyper echogenecity	Number of patients
≤0.1cm ²	9
0.11- 0.15	12
0.16- 0.2	18
0.21- 0.25	6

Table No 4: Volume of left SN Hyper echogenecity

Volume of left SN Hyper echogenecity	Number of patients
≤0.08	0
0.09- 0.1	3
0.11- 0.12	4
0.13- 0.14	4
0.15- 0.16	4
0.17- 0.18	6
0.19-0.2	8
0.21- 0.22	8
0.23- 0.24	8

V. Discussion

In this study the most common self-reported autonomic symptoms noted on SCOPA –AUT Questionnaire were constipation, urinary urgency & light headed after standing for a while. Similar findings were reported in Abbott RD et al. study⁽⁵⁾ and the pathological basis is consistent with the Braak hypothesis.⁽⁶⁾

There was significant relationship between SCOPA –AUT sum score, GI, and GU scores with disease severity, whereas CV and TH scores of SCOPA showed no relation with H&Y stage in this study.

Out of SCOPA sub score, nocturia and light headed after standing for a while symptoms had significant correlation with quality of life.

Gastrointestinal and urinary domains of SCOPA are most frequent appeal symptoms and highly related with activity of daily living in PD patients and this is similar to study of Hobson et al., 2003; Verbaan et al., 2007.^(7,8) Orthostatic hypotension is one of the common symptoms of PD and is reported 20– 50% in PD patient (Pfeiffer, 2007, Dubow, 2007;)^(2,9). Usually orthostatic hypotension is observed more frequently in advanced disease stage. However, orthostatic hypotension and disease severity had no relation in this study. It is possible that the frequency of orthostatic hypotension is not always proportional with severity of motor dysfunction in these early stages of PD. Many patients who have severe orthostatic hypotension do not complain of their symptoms or vice versa.

There was no correlation between SCOPA score, which based on evaluation of subjective symptoms of autonomic function and objective autonomic function tests.

The prevalence of orthostatic hypotension in PD previously reported in the literature has varied but a recent meta-analysis of 25 studies calculated a prevalence of 30% with large statistical heterogeneity between studies,⁽¹⁰⁾ likely due to the type of study, participants and methodologies employed. Furthermore, some patients do not have symptoms even though they have orthostatic hypotension, and as a result it is not recognized by clinicians.

In our study AFT showed the prevalence of Parasympathetic dysfunction in 53% & sympathetic dysfunction in 31% of in cohort of PD patients. Parasympathetic dysfunction was found in patients even with low SCOPA-AUT sum scores depicting the importance of AFT testing in every IPD patient irrespective of having low /nil SCOPA-AUT score or complaints related autonomic function. This result is consistent with other studies that compare the results of autonomic dysfunction using SCOPA and autonomic function tests. (Schrezenmaier et al., 2005; Papapetropoulos et al., 2006)^(11,12).

These findings suggest that careful inquiry of autonomic dysfunction and evaluation with both qualitative and quantitative autonomic tests could be used as sensitive clinical indices for disease progression.

The overall parasympathetic dysfunction and sympathetic dysfunction picked up on results of AFT were more in tremor predominant patients compared to rigidity predominant PD patients with significant p value of 0.001 in respect to parasympathetic and 0.003 with sympathetic dysfunction respectively.

There was no significant correlation between SN echogenicity volumes and clinical features of IPD patients in our study. Previous studies have suggested that SN hyperechogenicity is associated with the disease severity, although the findings are conflicting.^(13,14)

In our study SN hyperechogenicity group was not significantly associated with age, H&Y stage, and duration of disease, as well as subjective (SCOPA) and objective autonomic dysfunction.

In this study tremor predominant IPD patients had more sum scores of PDQ39 , SCOPA-AUT & also found to have significant autonomic dysfunction on AFT.

In current study there is no differences in SN volumes between tremor dominant subtype and rigidity predominant subtype. This may be because almost the corresponding volume of SN hyperechogenicity was moderately enlarged in 93% of PD patients in our study. This implies larger number of PD subtype patients are needed for further analysis.

Significant Laterality index (larger SN/smaller SN >1.15) was found in 38 out of 45 (84.44%). Also

there was no significant correlation between tremor and rigidity groups in terms of Transcranial Ultra Sound volumes of SN or in values of Laterality index.

Together with these study findings, one could speculate that the echogenic pattern of SN might not be related to the progression of the disease. Some have failed to show any relation between SN hyperechogenicity and clinical severity like that of our study ⁽¹⁵⁾. SN echogenicity may remain stable at long-term follow up despite disease progression, and may even remain stable in those cases with rapid progression of clinical symptoms.

(16,17)

In our study patients with autonomic dysfunction had higher PDQ39 sum scores which indicates low quality of life. This is in correlation with previous studies that showed significant decrease in quality of life, and impose a major financial burden.

Like other non-motor symptoms, autonomic dysfunction in PD patients seriously limits physical activities, decrease quality of life, and impose a major financial burden (Pfeiffer, 2007) ⁽²⁾.

Several studies have shown the diagnostic potential of TCS in neurodegeneration. ^(18,14) However, the causes underlying SN hyperechogenicity as the most specific feature of iPD and its pathophysiologic meaning are unclear.

In this study the volumes of Substantia nigra are moderately enlarged in 93% of PD patients. Volume of right Substantia Nigra > 0.2 cm² is seen in 6 out of 45 patients (13.33 %). Volume of left Substantia Nigra >

0.2 cm² is seen in 16 out of 45 patients (35.55%). Bilateral enlargement of Substantia Nigra > 0.2 cm² is seen in 3 (6.66%).

Marked laterality defined by the laterality index as larger SN/smaller SN > 1.15. Laterality index (larger SN/smaller SN > 1.15) was found in 38 out of 45 (84.44%).

In a previous study marked laterality as measured by the laterality index (larger SN/smaller SN > 1.15) was found in 69% of iPD patients (54), whereas in our study was found in 38 out of 45 IPD patients (84.44%). SN echogenicity did not have any relation to age, sex or disease duration.

VI. Conclusions:

Most common self-reported autonomic symptoms noted on SCOPA – AUT Q were of GI (Constipation), GU & Light headed after standing for a while. SCOPA-AUT GI & GU scores as well as SCOPA-AUT Total score increased with increasing H & Y stages. AFT showed Parasympathetic dysfunction in 53% & sympathetic dysfunction in 31%. Tremor predominant IPD patients had more sum score of PDQ39 and SCOPAAUT, significant autonomic dysfunction on AFT. There was no correlation/ differences between tremor and rigidity groups in TRUS volumes of SN / Laterality index. TCUS allows diagnosis early in the disease course and in differential diagnosis. PDQ39 Score groups had significant differences between groups, with higher score having higher autonomic dysfunction but no relation was found with TCUS findings.

Based on our and previous studies we recommend objective autonomic function evaluation in every patient of IPD and the transcranial Doppler ultrasound evaluation to confirm and differentiate IPD from atypical parkinsonism syndromes.

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