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Original Research Article

Autonomic nervous system dysfunction in Parkinson's disease patients

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ABSTRACT

Background: Parkinson's disease (PD) PD ranks second among the common neurodegenerative disease next only to Alzheimer's dementia. Autonomic symptoms in Parkinson's disease is very common. This study assesses the autonomic dysfunction in PD, their prevalence, type and severity in related to staging.
Methods: The study was conducted in Rajiv Gandhi government general hospital, Institute of neurology Madras medical college between 2011 to 2013, 141 patients fulfilling the criteria of Parkinson's disease brain bank society were included in the study. All the patients were clinically examined with special attention to history, clinical features and symptoms and signs of Autonomic dysfunction. The patients were graded using the Hoehn and Yahr staging system.
Results: Among 141 patients, 118 (83.7%) had autonomic dysfunction. Among 87 males, 72 patients had ANS dysfunction and among 54 females, 46 patients had ANS dysfunction. Stage wise 39 patients of 53 patients (73.6%) belonging to Stage I; 37 of 44 (84.1%) belonging to Stage II; 26 of 28 (92.8%) belonging to Stage III and all patients belonging to Stage IV and V had ANS dysfunction.
Conclusions: ANS dysfunction in Parkinson's disease is a common problem and the prevalence of it is 82.75% in males and 85.2% in females and overall in 83.7% of patients. The prevalence of ANS dysfunction in Males and females increases as the Hoehn and Yahr stage increases as evidenced by 68.7% of males and 80.9% of females have ANS dysfunction in stage I, while 100% of males and females in stage IV and V have ANS dysfunction. Sexual dysfunction (84.7%) ranks first followed by gastrointestinal (56.9%), and thermoregulatory (51.3%) autonomic disturbances in males and urinary disturbances (78.3%), ranks first followed by thermoregulatory (65.2%), and cardiovascular disturbances (56.5%) in females.

Keywords: Autonomic dysfunction, Hoehn and yahr stage, Parkinson's disease

INTRODUCTION

Parkinson's disease (PD)[1] is a chronic neurodegenerative progressive neurological disease with clinical features viz rigidity, bradykinesia, rest tremor and postural instability. Asymmetry is a prominent feature of this diseased ranks second among the common neurodegenerative disease next only to Alzheimer's dementia.

The pathological characteristic of PD is intraneuronal alpha synuclein positive Lewy bodies and loss of neuronal cell. Apart from classical motor symptoms PD patients also develop non-motor symptoms. Non-motor symptoms cause a major disability in PD and the prominently contribute to decreasing quality of life especially in advanced stages of disease. The major non-motor symptoms are olfactory loss, psychiatric disturbances of depression and anxiety, sleep disorders,

cognitive dysfunction, and chiefly the Autonomic Dysfunction.[1-3]

Autonomic dysfunction in PD patients is being recognized since the original description by James Parkinson in 1817. Although severe ANS dysfunction is mostly seen with advanced PD, it is present in PD patients even in the early stages of the disease.[4] The symptoms of ANS dysfunction, mainly orthostatic hypotension and excessive sweating greatly compromise the quality of life of patients.

James Parkinson described abnormalities of salivation and sweating, and dysfunction of the alimentary tract and urinary bladder in PD. Patients rarely volunteer symptoms of autonomic disturbance in clinic, and perhaps because of this, there has been little interest in autonomic dysfunction in PD until recent years. Demonstration of the importance of dysautonomia in Parkinsonism patients, led to a recent resurgence in this area. The introduction of standardised diagnostic criteria for PD has improved diagnostic accuracy, and reports since the introduction of these guidelines continue to suggest that between 50% and 80% of subjects have objective evidence of autonomic involvement. The advances in management of this autonomic symptoms stresses the need for identification of autonomic symptoms early and improve the quality of life.

Hence, we have undertaken this study to assess the autonomic dysfunction in PD, their prevalence, early identification and clinical testing, so as to diagnose early autonomic dysfunction, in order that suitable treatment may be initiated to improve quality of life.

METHODS

The main aims of the study were to evaluate the prevalence of autonomic nervous system dysfunction symptoms in Parkinson's disease; To assess the prevalence and the impact Of age, sex, duration of PD on severity of autonomic dysfunction; To assess the correlation of Hoehn And Yahr staging of Parkinson's disease and autonomic dysfunction; and to correlate the prevalence of cardiovascular autonomic nervous system dysfunction in PD patients based on basic cardiovascular autonomic function tests with that of staging. The study was conducted in Institute of Neurology Madras Medical College Chennai, Tamil Nadu, India. during 2011 to 2013.

The study had been approved by Ethical Committee of Medical Faculty Madras Medical College Chennai, Informed and written consent were obtained in patient's own language before their inclusion in the study. 141 patients fulfilling the criteria of Parkinson's disease brain bank society[5,6] were included in the study. They constitute both the outpatients and inpatients of our hospital.

Inclusion criteria

All the patients fulfilling the criteria of Parkinson's Disease Society Brain Bank[5,6] were included in the study.

Exclusion criteria

All the patients with other central or peripheral nervous system disease, Parkinson plus syndromes, systemic diseases and drugs that are known to cause ANS dysfunction were excluded from the study.

The patients were diagnosed based on the following Parkinson's disease society brain bank criteria.[5,6]

All the patients were clinically examined with special attention to history, clinical features and symptoms and signs of autonomic dysfunction. The patients were graded using the Hoehn and Yahr staging system.

Hoehn And Yahr Staging[1]

- Stage I: Only unilateral involvement, usually with minimal or no functional disability
- Stage II: Bilateral disease or midline involvement without impairment of balance
- Stage III: Mild to moderate bilateral disease with impaired postural reflexes; physically independent
- Stage IV: Severe disabling disease; still able to walk or stand unassisted
- Stage V: Wheel chair bound or confinement to bed unless aided.

All the patients were questioned about autonomic symptoms under various categories gastrointestinal, urinary, cardiovascular, thermoregulatory and sexual dysfunction and tabulated based on their presence. A number of drugs influence the results of autonomic testing such as anticholinergics adrenergic antagonists (β-blocker), sympathomimetic, Para sympathomimetic, and drugs. Affecting blood volume (diuretics and fludrocortisone). These drugs were discontinued before autonomic testing in consultation with the primary physician. The patient abstained from alcohol, tea, and coffee for at least 3 hours and preferably 12 hours. Patient were examined in rested and relaxed condition. All patients were subjected to complete general and neurological examination, Compressive dressings such as elastic stocking were removed before the test. Patients with heart failure, obstructive lung disease, atrial fibrillation, and sicca syndrome were excluded. The following cardiovascular autonomic function tests were done for all the patients after excluding other causes.

Important tests used for evaluation of autonomic functions

Tests of cardiovascular autonomic system regulation[7,8]

Cardiovascular response on standing and Heart rate variability(HRV) 30:15 R-R ratio.[7,8] HRV with respiration (sinus arrhythmia; R-R-interval analysis).

Cardiovascular responses to standing and 30:15 R-R ratio[7-10]

Blood pressure changes on standing are studied to assess the integrity of the sympathetic system and heart rate changes of parasympathetic cholinergic (cardiovagal) functions. Normally, on standing, exercise reflex and mechanical effects on venous capacitance and arterial resistance vessels become operative in addition to gravitational changes (Ewing et al).[11] BP and Heart rate are measured after a rest of 20 minutes initially. BP and heart rate are measured at baseline and then serially for 1-3 min after standing. ECG allows determination of 30:15 R-R ratio, i.e. the longest R-R interval (slowest heart rate) occurring about 30 beats after standing divided by the shortest RR interval (fastest heart rate), which occurs about 15 beats after standing (Ewing et al).[11]

The diagnosis of orthostatic hypotension is based on a fall of at least 20mmHg systolic or 10 mm of diastolic BP on assuming erect posture but some authorities allow more than 30 mm systolic and 20 mm diastolic BP. The 30:15 R-R ratio is normally greater than 1.04 and abnormal if less than 1.0 (Ewing et al).[11] The age-related normal values of R-R ratio are 30-49 years: 1.09; 50-65 years: 1.03.

Heart rate variation with respiration (Sinus arrhythmia, R-R Interval analysis)[8,12,13]

The study of heart rate variation with respiration is indicated for testing the integrity of parasympathetic cholinergic functions.[8] The variation of heart rate with respiration is known as sinus arrhythmia.[12,14,15] Inspiration increases and expiration decreases the heart rate.

A simple protocol for studying sinus arrhythmia is putting the patient supine with head elevated to 30° and breathing deeply at a rate of 6/min, allowing 5 s each for inspiration and expiration. The maximum and minimum heart rate with each respiratory cycle and mean variation are determined. Heart rate variability(HRV) ratio is determined as the sum of six longest R-R intervals, divided by the sum of six shortest R-R intervals.[8,15] Normal values for single deep breath E-I ratio at different age are 41-50 years > 1.12, 51-60 years >1.09, 61-70 years >1.07. The advantage of studying sinus arrhythmia is that it is sensitive and can be easily carried out on most EMG equipments.[8,15]

Valsalva manoeuvre and valsalva ratio[16,17]

Valsalva manoeuvre helps in assessing the parasympathetic cholinergic functions. Valsalva manoeuvre has four phases.

The patient lies supine with head elevated to 30°. The patient strains for 15s against by blowing 40 mmHg through a mouthpiece to a sphygmomanometer. Following stopping of the valsalva strain, the patient relaxes and breathes normally. The ECG is monitored during the strain and 30-45s following its release. The maximum heart rate of phase II actually occurs about 1 s following cessation of strain, which is generally taken as the maximum heart rate. The minimum heart rate occurs about 15-20s after releasing the strain. The ratio of maximum to minimum heart rate is calculated by repeating the procedure 3 times.

Blood pressure response to isovolumetric exercise

Sustained muscular contraction causes increased BP and heart rate as a result of exercise reflex, which reduces parasympathetic and increases sympathetic activity. Sympathetic adrenergic function is responsible for blood pressure changes and the parasympathetic cholinergic function is responsible for HR changes. In this test, the patient maintains a grip of 30% of maximum voluntary activity for 3-5 min. Normally, the diastolic BP will rise more than 15 mmHg. This test is relatively independent of age (Ewing et al).[11]

Blood Pressure to mental arithmetic[16,17]

Blood pressure response to mental stress such as arithmetic, sudden noise or emotional stress can result in increase in BP and heart rate due to excessive sympathetic outflow. It is a useful test of sympathetic efferent function.

Cold Pressor Test[16,17]

The patient submerges one upper limb in ice cold water for 60s, which results in rise of systolic BP by 15-20 mmHg and diastolic by 10 mmHg. The afferent limb of the test is somatic and efferent sympathetic.

Autonomic Function Tests

- Blood pressure in supine and standing after 3 minutes
  Abnormal: Postural fall of SBP > 20 mm of Hg and DBP >10 mm of Hg
- Blood pressure response to sustained handgrip
  Abnormal: DBP <10 mm of Hg, Normal: DBP >15 mm of Hg
- BP variation to mental arithmetic
  Abnormal: DBP <10 mm of Hg, Normal: DBP >15 mm of Hg
- BP variation to cold pressor test
  Abnormal: DBP <5 mm of Hg, Normal: DBP >10 mm of Hg
- Heart rate variability ratio to standing
  Abnormal: < 1.04
- Heart rate variability ratio to valsalva

Abnormal: <1.2

- Heart rate variability ratio to deep breathing
  Abnormal: <1.0.

The following results were considered as abnormal in cardiovascular autonomic function tests.

Valsalva ratio of less than 1.2 is regarded as abnormal, 1.2-1.45 as borderline and greater than 1.45 as normal (Ewing, 1976). Valsalva ratio decreases with age. The age specific norms are more precise: 41-60 years > 1.45, 61-70 years >1.35 (Low, 2004).[16,17]

Normal values for single deep breath E-I ratio at different age are 41-50 years > 1.12, 51-60 years >1.09, 61-70 years >1.07.

Patients with ANS system were graded in severity depending on the number of systems involved. The systems include gastrointestinal, urinary, cardiovascular, thermoregulatory and sexual dysfunction, the results were graded as follows.

- *Mild:* Involvement of One to two systems
- *Moderate:* Involvement of Three systems
- *Severe:* Involvement of More than three systems.

The results were analysed through SPSS version 20 (Statistical Package for the Social Sciences or Superior Performing Statistical Software) statistical analysis by Pearson Chi-square test and p values obtained.

RESULTS

A total of 141 patients of Parkinson's disease, both inpatients and outpatients of Rajiv Gandhi Govt. General Hospital, Institute of Neurology Madras Medical College between 2011 to 2013, were analysed and the results of analysis are as follows.

Among 141 patients enrolled males were 87 in number and females were 54 in number. The mean age of male patients was 54, and female was 52. The highest age among male patients was 70 and the lowest age was 40.

The patients were grouped as follows. Patients were classified based on Hoehn and Yahr staging Stage I to V. Stage IV and V were grouped into one as the number of patients was less. 53 patients viz 32 males and 21 females belonged to Stage I of Parkinson's disease; 44 patients viz 25 males and 19 females belonged to Stage II of Parkinson's disease; 28 patients viz 18 males and 10 females belonged to Stage III of Parkinson's disease; 16 patients viz 12 males and 4 females belonged to Stage IV of Parkinson's disease.

Among 141 patients, 118 (83.7%) had autonomic dysfunction. Among 87 males, 72 patients had ANS dysfunction and among 54 females, 46 patients had ANS dysfunction.

Table 1: Sexwise involvement of ANS dysfunction.

Sex	Total PD patients	Patients with ANS dysfunction
Males	87	72 (82.75%)
Females	54	46 (85.2%)
Total	141	118 (83.7%)

Stage wise 39 patients of 53 patients (73.6%) belonging to Stage I; 37 of 44 (84.1%) belonging to Stage II; 26 of 28 (84.1%) belonging to Stage III and all patients belonging to Stage IV and V had ANS dysfunction.

Among 32 patients belonging to Stage I Parkinson's disease, 22 had ANS dysfunction, and 21 out of 25 belonging to Stage II, 17 out of 18 belonging to Stage III and all patients of Stage IV and V (100%) had autonomic dysfunction. Among 21 females of Stage I Parkinson's disease, 17 had ANS dysfunction, and 16 out of 19 belonging to Stage II, 9 out of 10 belonging to Stage III and all patients of Stage IV (100%) had autonomic dysfunction.

Table 2: Stage wise correlation with severity of ANS dysfunction depicting more severity in stage III and IV.

Staging	Total no. of patients	Patients with ANS dysfunction	% of patients with ANS dysfunction
Stage I	53	39	73.6
Stage II	44	37	84.1
Stage III	28	26	92.9
Stage IV and V	16	16	100
Total	141	118	83.7

Among 118 patients, 61male and 21 female had sexual dysfunction, 34 males and 36 females had urinary dysfunction, 41 males and 22 females had gastrointestinal tract dysfunction, 27 males and 26 females had cardiovascular dysfunction, 37 males and 30 females had thermoregulatory dysfunction. Patients had ANS dysfunction in multiple categories.

Table 3: Systemise involvement of ANS dysfunction.

Categories	Males	Females
Sexual	61 (84.7%)	21 (45.7%)
Urinary	34 (47.2%)	36 (78.3%)
GIT	41 (56.9%)	22 (47.8%)
Cardiovascular	27 (37.5%)	26 (56.5%)
Thermoregulatory	37 (51.3%)	30 (65.2%)

In 40-50 years age group, 38.6% (n-22) did not have ANS dysfunction; 49.1% had mild ANS dysfunction; 12.3% had mild ANS dysfunction; none had severe ANS dysfunction. But on the contrary in 60-70 age group, 12.8% had moderate ANS dysfunction and 94.4% severe ANS dysfunction. There are no patients without ANS dysfunction and mild dysfunction. On analyzing sex with severity of dysfunction, among males 17.2% (n-15) did not have ANS dysfunction; 27.6% (n-24) had mild ANS dysfunction; 26.4% (n-23) had moderate ANS dysfunction; 28.7% (n-25) had severe ANS dysfunction. In females 14.8% (n-8) did not have ANS dysfunction; 27.8% (n-15) had mild ANS dysfunction; 37.0% (n-20) had moderate ANS dysfunction; 20.4% (n-11) had severe ANS dysfunction. HRV was done on standing and the results based on staging are 53 patients (100%) had normal HRV in stage I, whereas in stage IV and V, only 6.2% had normal HRV and 93.8%% had abnormal HRV on standing. HRV was done on valsalva and the results based on staging are 53 patients (100%) had normal HRV in stage I whereas in stage IV and V all 16 patients (100%) had abnormal HRV on respiration. HRV was done on respiration and the results based on staging are 53 patients (100%) had normal HRV in stage I, whereas in stage IV and V, only 6.2% had normal HRV and 93.8% had abnormal HRV on respiration.

Table 4: Stage wise correlation with heart rate variability ratio on respiration.

			HRV on respiration		Total	
			Normal	Abnormal		P value
Staging	**I**	**Count**	53	0	53	
		% of patients within same Staging	100.0%	0%	100.0%	<0.0001
		% of patient within same status of normal/abnormal within HRV on respiration	53.0%	0%	37.6%	<0.0001
	II	**Count**	38	6	44	
		% of patients within same Staging	86.4%	13.6%	100.0%	<0.0001
		% of patient within same status of normal/abnormal within HRV on respiration	38.0%	14.6%	31.2%	<0.0001
	III	**Count**	8	20	28	
		% of patients within same Staging	28.6%	71.4%	100.0%	<0.0001
		% of patients within same status of normal/abnormal within HRV on respiration	8.0%	48.8%	19.9%	<0.0001
	IV and V	**Count**	1	15	16	
		% of patients within same Staging	6.3%	93.8%	100.0%	<0.0001
		% of patient within same status of normal/abnormal within HRV on respiration	1.0%	36.6%	11.3%	<0.0001
Total		**Count**	100	41	141	
		% of patients within same Staging	70.9%	29.1%	100.0%	

DISCUSSION

A total of 141 patients both inpatients and outpatients of Rajiv Gandhi government general hospital, institute of neurology madras medical college between 2011 and 2013 with clinical feature suggestive of Parkinson's disease were analysed. Among 141 patients enrolled in the study 87 were males and 54 were females with the ages ranging from 40-70 years in males and females.

The mean age of males and females were 54 years and 52 years respectively. 57 (40.4%) of patients were in the age group of 40years to 50 years; 45 (31.9%) of patients were in the age group of 51 years to 60 years; 39 (27.7%) of patients were in the age group of 61 years to 70 years.

On classification based on staging, 53 patients viz 32 males and 21 females belonged to Stage I of Parkinson's Disease; 44 patients viz 25 males and 19 females belonged to Stage II of Parkinson's Disease; 28 patients viz 18 males and 10 females belonged to Stage III of Parkinson's disease; 16 patients viz 12 males and 4 females belonged to Stage IV and V of Parkinson's disease.

Overall 118 out of 141 patients (83.7%) of patients had ANS dysfunction. Among 87 males, 72 patients (82.75%)

had ANS dysfunction and among 54 females, 46 patients (85.2%) had ANS dysfunction. Singer et al noted that 89% of Parkinsonian patients had at least one of the autonomic symptoms. 80-90 % of PD patients have some ANS symptoms as per Turkka et al.[18] This is consistent with current study where ANS symptoms were present in 83.7% of PD patients.

Among male patients, 22 out of 32 (68.75%) belonging to Stage I; 21 out of 25 (84%) belonging to Stage II, 17 out of 18 (94.4%) belonging to Stage III and all patients (100%) of Stage IV had autonomic dysfunction. Among female patients, 17 out of 21 (80.9%) belonging to Stage I ;16 out of 19 (84.2%) belonging to Stage II, 9 out of 10(90%) belonging to Stage III and all patients (100%) of Stage IV had autonomic dysfunction. Overall stage wise 39 patients of 53 patients (73.6%) belonging to Stage I; 37 of 44 (84.1%) belonging to Stage II; 26 of 28 (84.1%) belonging to Stage III and all patients (100%) belonging to Stage IV and V had ANS dysfunction. Hence as the staging of PD increases the prevalence of ANS dysfunction increases both in males and females. Thus ANS dysfunction significantly correlates with staging of PD in both sexes which is similar with studies of Zesiewicz TA et al and Kim JB et al in their series.[19,20]

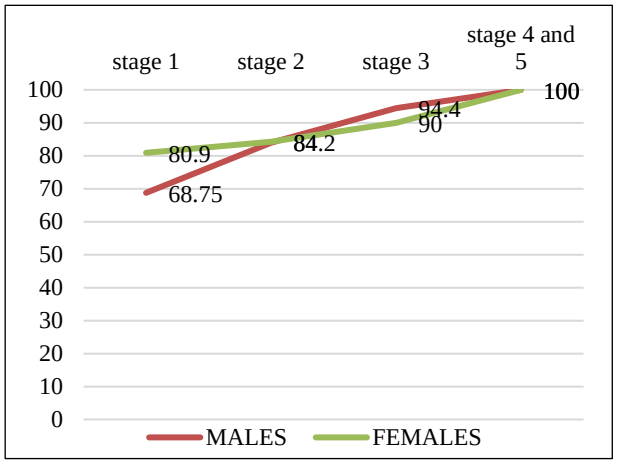

Figure 1: Depicts increasing prevalence of ANS dysfunction as stage increases.

Among 118 patients, 61 males (84.7%) and 21(45.7%) female had sexual dysfunction, 34 males (47.2%) and 36 females (78.3%) had urinary dysfunction, 41 males (56.9%) and 22 females (47.8%) had gastrointestinal tract dysfunction, 27 males (37.5%) and 26 females (56.5%) had cardiovascular dysfunction,37 males (51.3%) and 30 females (65.2%) had thermoregulatory dysfunction. Patients had ANS dysfunction in multiple categories and the percentages observed were within same gender.

Among male's sexual dysfunction was the most common ANS dysfunction followed by gastrointestinal tract dysfunction, thermoregulatory dysfunction, urinary dysfunction, and cardiovascular dysfunction in that order. Among female's urinary dysfunction was the most common followed by thermoregulatory dysfunction and cardiovascular dysfunction. Wullner U et al in his analysis of Autonomic dysfunction in 3414 Parkinson's disease patients have reported Orthostatic hypotension in 10% of women and 11% of men, urinary incontinence in 22% of women and 21% of men, sexual dysfunction in 8% of women and 30% of men (50% of whom reported erectile dysfunction).[21] According to Singer C et al, who evaluated autonomic function in forty-eight men with Parkinson's disease (PD), found a higher prevalence of the following symptoms of autonomic dysfunction in the PD patients: erectile dysfunction (60.4 versus. 37.5%), sensation of incomplete bladder emptying (41.6 versus. 15.6%), urgency (45.8 versus. 3.125%), constipation (43.9 versus. 6.25%), dysphagia (22.9 versus. 6.25%) and orthostatic dizziness (21.95 versus. 0%). Sexual dysfunction ranks first similar to this study.[22]

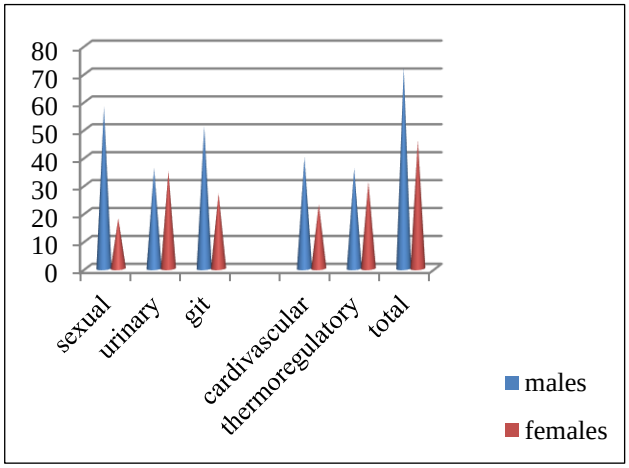

Figure 2: Prevalence of system wise ANS dysfunction in PD patients both males and females.

On correlating the age with ANS dysfunction, in 40- 50 group,22 (38.6%) did not have ANS dysfunction 28 (49.1%) had mild ANS dysfunction 7 (12.3%) had moderate ANS dysfunction and none had severe dysfunction. In 50-60 age group, 1 (2.2%) did not have ANS dysfunction, 11(24.4%) had mild ANS dysfunction, 31 (68.9%) had moderate ANS dysfunction and 2 (4.4%) had severe dysfunction. In 60-70 age group, 5 (12.8%) had moderate ANS dysfunction and 34 (87.2%) had severe dysfunction. In initial years of the disease, patients did not have ANS dysfunction or only mild to moderate ANS dysfunction only. But as the age advances the severity of dysfunction increases, which is statistically significant (p value<0.0001). There is no significant correlation between males and females regarding the severity of ANS dysfunction.

On analysing the disease duration with ANS dysfunction, in upto 5 years group,14 (25%) did not have ANS dysfunction, 35 (62.5%) had mild ANS dysfunction 7 (12.5%) had moderate ANS dysfunction and none had severe dysfunction. In 5-7.5 years group, 7 (16.7%) did not have ANS dysfunction, 4 (9.5%) had mild ANS

dysfunction, 29 (69%) had moderate ANS dysfunction and 2 (4.8%) had severe dysfunction. In 7.5-10 years group, 2 (8.3%) did not have ANS dysfunction 5 (20.8%) had moderate ANS dysfunction and 17 (70.8%) had severe dysfunction. In more than 10 years group,2 (10.5%) had moderate ANS dysfunction and 17 (89.5%) had severe dysfunction. As the disease duration advances the severity of dysfunction increases, with patients in older age group having disease duration more than 10 years have moderate to severe ANS dysfunction and which is statistically significant (p value<0.0001).

Table 5: Disease duration in years correlation with severity of ANS dysfunction.

			Severity				Total	
			Nil	Mild	Moderate	Severe		P-value
Disease duration in years	**Upto 5**	**Count**	14	35	7	0	56	
		% of patients within same duration group	25.0%	62.5%	12.5%	.0%	100.0%	<0.0001
		% of patients within same severity grading	60.9%	89.7%	16.3%	.0%	39.7%	<0.0001
	5-7.5	Count	7	4	29	2	42	
		% of patients within same duration group	16.7%	9.5%	69.0%	4.8%	100.0%	<0.0001
		% of patients within same severity grading	30.4%	10.3%	67.4%	5.6%	29.8%	<0.0001
	7.5-10	Count	2	0	5	17	24	
		% of patients within same duration group	8.3%	0%	20.8%	70.8%	100.0%	<0.0001
		% of patients within same severity grading	8.7%	.0%	11.6%	47.2%	17.0%	<0.0001
	Above 10	Count	0	0	2	17	19	
		% of patients within same duration group	0%	0%	10.5%	89.5%	100.0%	<0.0001
		% of patients within same severity grading	0%	0%	4.7%	47.2%	13.5%	<0.0001
Total		**Count**	**Count**	39	43	36	141	
		% of patients within same duration group	% of patients within same Age group	27.7%	30.5%	25.5%	100.0%	

On analysing the staging with severity of ANS dysfunction, in Stage I, 14 (26.4%) patients did not have ANS dysfunction, 33 (62.3%) had mild ANS dysfunction 6 (11.3%) had moderate ANS dysfunction and none had severe dysfunction. In Stage II, 7 (15.9%) did not have ANS dysfunction, 6 (13.6%) had mild ANS dysfunction, 30 (68.2%) had moderate ANS dysfunction and 1 (2.3%) had severe dysfunction. In Stage III, 2 (7.1%) did not have ANS dysfunction 7 (25%) had moderate ANS dysfunction and 19 (67.9%) had severe dysfunction. In Stage IV and V, all 16 patients (100%) had severe dysfunction. As the staging advances the severity of dysfunction increases. All patients in Stage IV and V patients had severe ANS dysfunction in all patients which is statistically significant (p value<0.0001).

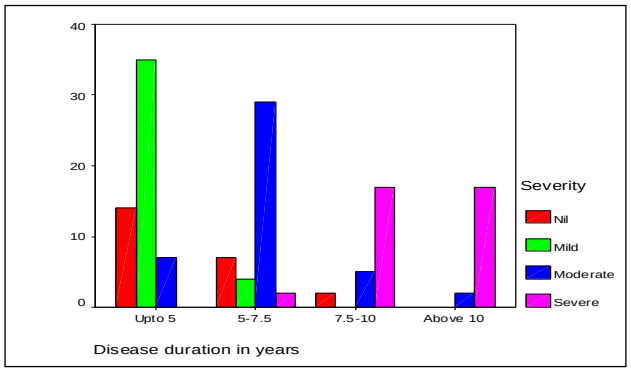

Figure 3: Illustrates more severe ANS dysfunction as disease duration increases.

Pospisil P and Konecny L et al in their study has concluded that autonomic nervous system dysfunction is more severe in advanced stages of Hoehn and Yahr (stages 2 and 3) than early stages (stage 1).[20] Hoehn and Yahr (H and Y) stage, disease duration, and age at onset all showed significant correlations with Autonomic dysfunction (Zesiewicz TA et al).[19]

On analysing various sympathetic tests, BP on cold pressor test, BP on isovolumetric exercise, BP on standing, BP on valsalva manoeuvre, as the stage worsens the abnormality of BP measurements increases and thus they all are significantly correlated with the staging and thus severity. Orthostatic hypotension makes the patients in terminal stages disabled.

Table 6: Hoehn and Yahr stage wise severity of ANS Dysfunction.

			Severity				Total	
			Nil	Mild	Moderate	Severe		P value
Staging	**I**	**Count**	14	33	6	0	53	
		% of patients within same Staging	26.4%	62.3%	11.3%	0%	100.0%	<0.0001
		% of patients within same severity grading	60.9%	84.6%	14.0%	0%	37.6%	<0.0001
	II	**Count**	7	6	30	1	44	
		% of patients within same Staging	15.9%	13.6%	68.2%	2.3%	100.0%	<0.0001
		% of patients within same severity grading	30.4%	15.4%	69.8%	2.8%	31.2%	<0.0001
	III	**Count**	2	0	7	19	28	
		% of patients within same Staging	7.1%	0%	25.0%	67.9%	100.0%	<0.0001
		% of patients within same severity grading	8.7%	0%	16.3%	52.8%	19.9%	<0.0001
	IV and V	**Count**	0	0	0	16	16	
		% of patients within same Staging	0%	0%	0%	100.0%	100.0%	<0.0001
		% of patients within same severity grading	0%	0%	0%	44.4%	11.3%	<0.0001
Total		**Count**	23	39	43	36	141	
		% of patients within same Staging	16.3%	27.7%	30.5%	25.5%	100.0%	<0.0001
		% of patients within same severity grading	100.0%	100.0%	100.0%	100.0%	100.0%	<0.0001

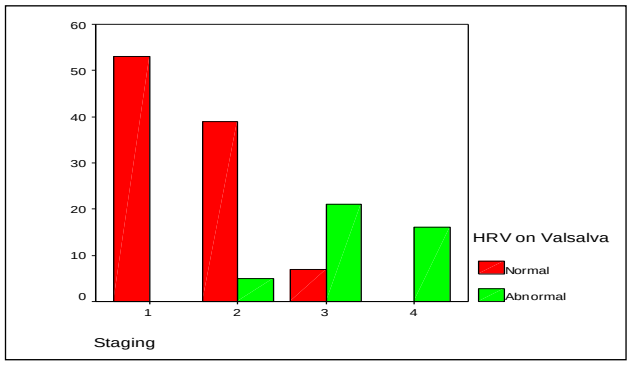

Figure 4: Stage wise correlation with HRV on valsalva depicting more normal ratio in stages I and II, more abnormal HRV in stage III and IV.

Similarly, on analysing parasympathetic cardiovascular function tests, Heart rate variability ratio(HRV) on standing, HRV on valsalva, HRV on respiration, were abnormal as the staging and disease worsens.

Meco et al in his study of Cardiovascular reflexes and autonomic dysfunction in Parkinson's disease analysed in 20 cases heart rate variation during normal respiration, standing and during the Valsalva manoeuvre and blood pressure variation after standing and concluded that significant changes in the different heart rate variation indices were found in the Parkinsonian patients that correlates with both the duration and severity of the extrapyramidal symptomatology.[23] These results were in consistent with current study. Ludin SM, and Steiger UH et al analysed cardiovascular reflexes in 22 patients and

have concluded the heart rate variation evoked by deep breathing as well as the blood pressure response and the heart rate response to sustained isometric exercise were significantly diminished in the patients with idiopathic Parkinson's disease.[24] Piha SJ, Rinne JO, Rinne UK et al in their study of Autonomic dysfunction in recent onset and advanced Parkinson's diseas Maetzler W et al and Goldstein DS et al, have concluded that in Parkinson's disease a parasympathetic damage occurs which worsens during the course of the disease, and also the orthostatic fall in blood pressure, indicating a sympathetic dysfunction.[25-28] The dysfunction of cardiovascular autonomic control is thought to correlate with the severity of the disease (Van Dijk et al).[29,30]

Hence, prevalence of ANS dysfunction is high in Parkinson disease patients. It correlates well with Age, Duration, Hoehn and Yahr staging. Cardiovascular autonomic function tests also correlate with staging and thus severity of disease. Advancement in management of autonomic symptoms stresses the need for identification of ANS symptoms early so that early treatment gives them good quality of life.

CONCLUSION

Autonomic nervous system dysfunction in Parkinson's disease is a common problem and the prevalence of it is 82.75% in males and 85.2% in females and overall in 83.7% of patients. The prevalence of ANS dysfunction in Males increases as the Hoehn and Yahr stage increases as evidenced by 68.7% of males have ANS dysfunction in stage I, while 100% of males in stage IV and V have ANS dysfunction. The prevalence of ANS dysfunction in Females increases as the Hoehn and Yahr stage increases as evidenced by 80.9% of females have ANS dysfunction in stage I, while 100% of Females in stage IV and V have ANS dysfunction. Sexual dysfunction (84.7%) ranks first followed by gastrointestinal (56.9%), and thermoregulatory (51.3%) autonomic disturbances in males and urinary disturbances (78.3%), ranks first followed by thermoregulatory (65.2%), and cardiovascular disturbances (56.5%), in females.

There is a significant correlation between the age and ANS dysfunction, as the age advances the severity of dysfunction also worsens, which is statistically significant (p value<0.0001). There is no significant correlation between the sex and severity of ANS dysfunction. As the disease duration advances the severity of dysfunction increases which is statistically significant (p value<0.0001). Patient with disease duration less than 5 years did not have ANS dysfunction or only mild dysfunction whereas with patients having disease duration more than 10 years have predominantly moderate to severe ANS dysfunction in all patients. There exists a significant correlation between Hoehn and Yahr staging and severity of ANS dysfunction. Patient in stage I did not have ANS dysfunction (26.4%) or only mild dysfunction (62.3%) whereas, all patients in stage IV and V have severe ANS dysfunction (100%). The prevalence of abnormality in Sympathetic cardiovascular autonomic function tests viz BP on cold pressor test, BP on isovolumetric exercise, BP on standing, BP on valsalva manoeuvre, increases as the stage worsens significantly. The prevalence of abnormality in Parasympathetic cardiovascular autonomic function tests viz Heart rate variability ratio (HRV) on standing, HRV on valsalva, HRV on respiration, also increases as the stage increases.

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