

Frequency and Predictors of Autonomic Dysfunction in Parkinson's Disease: A Study of African Patients in Lagos, Nigeria.

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The degenerative changes in PD also affect the autonomic nervous system. The frequency and predictors of such involvement in Africans with PD has not been reported.

Objective

- i) To determine the frequency and type of autonomic dysfunction in Nigerians with idiopathic Parkinson's disease (PD)
- ii) To determine the predictors of autonomic dysfunction in PD

Methods

Cardiovascular autonomic function assessed in 33 study subjects with PD and 33 age-matched controls, utilising heart rate variability to deep breathing, standing and the Valsalva manoeuvre, and the blood pressure (BP) response to standing. The results were compared based on treatment category, grade of severity on the Columbia scale of Hoehn and Yahr, duration of PD, age at onset of PD, present age and occurrence of autonomic symptoms

Results

Parasympathetic function was abnormal in 51.5% of PD subjects, significantly higher than controls ($P < 0.001$). Of these, 76.5% had early parasympathetic involvement and 23.5% definite parasympathetic involvement. Age above 65 years (at time of study or onset of PD) was the only clinical variable associated with parasympathetic autonomic dysfunction ($p < 0.05$). Symptoms dysfunction occurred in 60.6% of PD patients and only 6.1% of controls ($p < 0.001$). There was however no demonstrable relationship between the occurrence of symptoms and objective evidence of autonomic dysfunction: 41.2% of PD patients with parasympathetic dysfunction had no symptoms.

Conclusion

Autonomic dysfunction was found to be common in Africans with PD, particularly those above 65 years and tends to affect the parasympathetic system. However, the abnormality may be detectable even before symptoms appear. As such, we recommend that cardiovascular tests of autonomic function be a routine aspect of the evaluation of PD patients, especially with advancing age.

Key Words: autonomic dysfunction, parkinson's disease, cardiovascular autonomic tests

The occurrence of autonomic dysfunction as one of the non-motor manifestations of Parkinson's disease (PD) was first reported in 1817 by James Parkinson^{1,2}. Despite this early description, physicians for many years either neglected autonomic symptoms in PD or attributed them to anticholinergic drugs which these patients received².

The pathologic substrate for occurrence of autonomic dysfunction in PD is the finding of pathognomonic Lewy bodies in the areas involved in autonomic regulation such as the locus ceruleus, raphe nuclei, various pontine and mesencephalic structures as well as the hypothalamus^{1,3-5}. In addition, Lewy bodies have been found in preganglionic structures of the sympathetic and parasympathetic nervous system. Post-ganglionic sympathetic neurons in the pre- and paravertebral ganglia also often contain Lewy bodies³⁻⁵.

The epidemiology of autonomic dysfunction in PD as described in various studies has differed. Although it is generally accepted that autonomic dysfunction involving virtually every aspect of the ANS occurs in PD, the precise prevalence is non-uniform. This non-uniformity is contributed to by the variations in patient selection criteria, methodology, duration or severity of the disease process, and medication at the time of the study⁶. Furthermore, various authors have concentrated on distinct aspect of the intrinsically diverse ANS in PD.

With regards to PD in Africans, there is a paucity of studies on autonomic function in PD. Osuntokun and Bademosi (1979) reported the finding of autonomic symptoms or signs in 31% of a cohort of patients with parkinsonism (including idiopathic PD and secondary parkinsonism)⁷. The present study evaluated autonomic function in PD patients using specific cardiovascular autonomic function tests.

Subjects and Methods

Sixty-six (66) subjects comprised 33 study subjects with neurologist-confirmed diagnosis of idiopathic PD attending the Neurology outpatient clinic of the Lagos University Teaching Hospital, Lagos, Nigeria, West Africa, and 33 age and sex-matched healthy controls were studied. The recruitment of the study subjects was on the basis of a total sampling technique and enrollment of all consecutively attending, consenting subjects who met the inclusion criteria for idiopathic PD. The inclusion criteria were as follows:

- a) The presence of at least any three of these cardinal features of PD (Tremors; Rigidity; Bradykinesia or Akinesia; Postural or Gait abnormality)
- b) Duration of symptoms of PD of at least six months
- c) Absence of any identifiable underlying aetiology of secondary parkinsonism
- d) Columbia scale of Hoehn and Yahr stage of severity I to III.

In addition, patients who had other diseases known to cause autonomic dysfunction were excluded from the study, as were patients on medication capable of interfering with autonomic function (but excluding antiparkinsonian medication).

The procedure for autonomic testing was carried out under the same environmental conditions for both study subjects and controls. A standard proforma was used to document personal details, as well as clinical characteristics including the age at onset of PD, duration of symptoms of PD and severity of clinical features on the Columbia scale of Hoehn and Yahr. Stages I and II diseases were further classified as mild disease, while stage III was regarded as moderate disease. Treatment category (treated or untreated PD), nature of drug therapy where relevant, and duration of such therapy, were also documented.

A questionnaire to detect the presence of recognised symptoms suggestive of autonomic dysfunction, including gastrointestinal, cardiovascular, genitourinary, thermoregulatory, and respiratory systems) was also administered on study subjects and controls.

Objective assessment of cardiovascular autonomic function was carried out on all the study subjects and controls using standard procedures as described by other authors⁸. All tests were carried out by one of the authors (ONU) assisted by an ECG technician. The subjects were pre-instructed not to take any medication for at least twelve hours prior to the investigations. The tests utilised were as follows:

- i) Heart rate response to standing
- ii) Heart rate response to deep breathing
- iii) Heart rate response to the Valsalva manoeuvre
- iv) Blood pressure response to standing

Autonomic function was regarded as normal if all four tests were normal or only one was borderline. Early parasympathetic dysfunction was present if one of the three heart rate tests was abnormal or two borderline. Definite parasympathetic dysfunction was diagnosed when two or more of the heart rate tests were abnormal. Combined parasympathetic and sympathetic dysfunction was said to occur when, in addition to abnormal parasympathetic test results, the BP test was abnormal⁹.

Statistical analysis

Data were expressed as means \pm standard deviation. For comparison of mean values of subjects and controls, the students' t-test was used. Differences in categorical variables were tested by Pearson's χ^2 test. A p values less than 0.05 was regarded as significant.

Results

There was a male predominance (25 males and 8 females) with a male to female ratio of 3.1 to 1. Age range of PD patients and controls was 39-80 years (mean 63.2 ± 10.2

years) and 40-76 years (mean 62.5 ± 10.3 years) respectively, with no significant difference between genders. Five (15.2%) of the study subjects had stage I disease, 15 (45.4%) had stage II disease and 13 (39.34%) had stage III disease. The other clinical characteristics are as shown in Table i.

Frequency of symptoms of autonomic dysfunction in study subjects and controls: The symptoms of autonomic dysfunction were documented in 20 (60.6%) PD patients, being significantly more frequent than in the controls (6.1%) ($p < 0.001$). The most common symptoms in study subjects were palpitations (12), constipation, postural dizziness and constipation (9 study subjects each).

Results of cardiovascular autonomic test in study subjects versus controls: All three tests of heart rate response (to deep breathing, the Valsalva manoeuvre and standing) showed abnormality that was statistically significant when study subjects were compared to controls (Figure 1) (Fischer exact p values < 0.001 , < 0.001 , < 0.005 for Valsalva ratio, deep breaths test, and standing test (30:15 ratio) respectively). The systolic BP test was abnormal in two each of subjects and controls (FEP > 0.05).

With regards to the clinical characteristics of the study subjects, there was no significant difference in occurrence of abnormal tests in the two treatment categories and in relation to disease severity. Abnormality in the deep breaths test occurred significantly more often ($p < 0.05$) in subjects (but not controls) aged 66-80 at the time of the study, and at onset of PD

Degree and nature of autonomic dysfunction in subjects and controls: Parasympathetic autonomic dysfunction occurred in 17 (51.5%) of the study subjects as compared to none of the controls ($p < 0.001$). The distribution of autonomic dysfunction is as shown in Figure 2. No study subject or control had combined (sympathetic and parasympathetic) dysfunction.

Relationship of autonomic dysfunction to clinical characteristics of study subjects: There was no significant difference in the occurrence of autonomic dysfunction based on duration of illness, severity of disease, treatment category or presence of symptoms of autonomic dysfunction (Table ii). However, significantly higher number of study subjects aged 66-80 years at the onset of PD ($P < 0.05$) and at the time of the study ($p < 0.005$) had autonomic dysfunction.

Table i: Clinical characteristics of study subjects

Characteristics	Number of subjects	Mean	SD
A)			
1 Age at onset of illness (years)	33	60.6	10.3
2 Duration of illness (months)			
All patients	33	28.6	22.1
Untreated PD	16	20.6	14.4
PD on treatment	17	40.9	25.6
B) Severity of PD			
	Number of subjects	% of total number (33)	
Mild disease (stages I & II)	20	60.6%	
Moderate disease (stage III)	13	39.4%	

Table ii: Predictors of Autonomic Dysfunction in Parkinson's disease

Clinical Variable	Total	Autonomic Dysfunction	Statistical Significance
A: Severity of PD			
Mild disease (stages I&II)	20	9	$\chi^2=1.46$; df=1;p=0.482
Moderate disease (stage III)	13	8	
B: Duration of PD			
≤ 24 months	19	11	$\chi^2=0.73$; df=1;p=0.392
> 24 months	14	6	
C: Treatment Category			
Treated	17	7	$\chi^2=1.50$; df=1;p=0.221
Untreated	16	10	
D: Present Age			
36-50 yr	5	2	$\chi^2=11.89$; df=2;p=0.003 (SIG)
51-65 yr	14	3	
66-80 yr	14	12	
E: Age at onset of PD			
36-50 yr	6	2	$\chi^2=7.64$; df=2;p=0.022 (SIG)
51-68 yr	15	5	
66-80 yr	12	10	
F: Symptoms*			
Present	20	10	$\chi^2=0.05$; df=1;p=0.829 (NS)
Absent	13	7	

* Symptoms of autonomic dysfunction

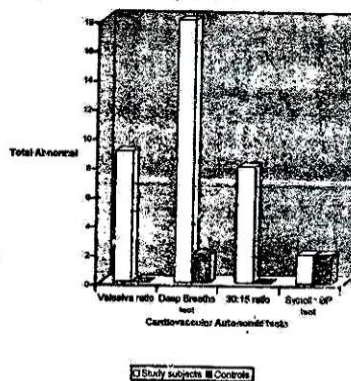


Figure 1: Comparison of results of cardiovascular autonomic tests in PD subjects and controls

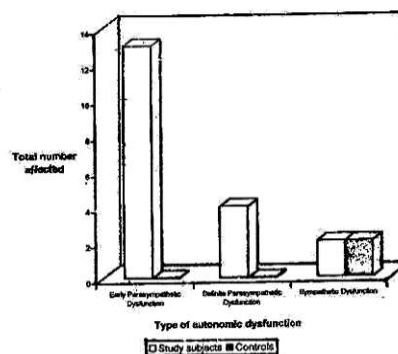


Figure 2: Nature and degree of autonomic dysfunction in study subjects compared to controls

Discussion

The age matching of subjects and controls was informed by the fact there are well-documented age related changes in autonomic function. As such, the determination of credibility of any findings would have to be based on comparison to age matched controls. Severity of illness was significantly related to the duration of illness ($p < 0.05$). Study subjects with longer duration of PD (> 24 months) had more severe disease. Thus, the only clinical variables found to be related in this study were duration of illness and the severity of illness on the Hoehn and Yahr scale.

Results of cardiovascular autonomic testing in PD

The results of the cardiovascular reflex tests clearly demonstrate abnormality in PD patients when compared to controls. The abnormalities were demonstrable in three of the tests, all representative of parasympathetic dysfunction in PD. The findings in the present study compare quite closely with those of other authors who found abnormalities in cardiovascular autonomic function in PD¹⁰⁻¹³. This is of particular relevance in this environment where there are hitherto no data to that effect. The data in the literature on the sympathetic system changes and on orthostatic hypotension in particular are widely differing^{12,14-15}. The deep breaths test was found to be the most specific test in detecting autonomic dysfunction in the present study.

Relationship of autonomic dysfunction to clinical variables

There was no demonstrable relationship between medication use and abnormalities in the tests. As such it is not possible to abrogate the abnormalities to the effect of medication. The existing literature fails to show any parasympathetic cardiovascular change after levodopa intake^{13,15}. The lack of an association between duration of PD and abnormal autonomic function is in contrast to findings by some other authors of marked reductions in the parasympathetic tests in patients with longer duration of illness^{11,12,16}. This difference may be attributed to the fact that most of these studies utilised patients with a longer mean duration of PD than the present study¹¹. The deep breaths test was the only test found to be related to the present age of the study subjects ($p < 0.05$). This finding is supported by an earlier report that the heart rate tests of parasympathetic function showed a decline with age which is more marked in PD than in controls¹⁰. The present study, unlike some earlier studies, did not demonstrate any significant relationship between severity of PD and abnormalities on cardiovascular reflex tests. The inclusion of PD patients with more severe disease in those studies may explain the finding. This view is supported by a similar finding of a greater degree of

abnormality in the cardiovascular reflex tests in advanced PD in a study which compared recent onset (stages I to III) disease to advanced (stage IV) disease¹².

Prevalence and nature of autonomic dysfunction in PD

Autonomic dysfunction occurred in 51.5% of Nigerian Africans with PD compared to 0% of controls ($p < 0.001$). The nature of autonomic dysfunction in PD was mainly parasympathetic. Carmelino *et al* who studied I and II disease described only parasympathetic dysfunction in their patients. Other authors have shown both parasympathetic and sympathetic dysfunction in PD¹⁰⁻¹². The defect found in the present study and others is in accordance with the known cell loss in the areas regulating the autonomic nervous function.

Despite the frequency of symptoms of autonomic dysfunction in PD patients in the present study, there was no relationship between presence of symptoms and demonstrable objective abnormality on cardiovascular testing. This emphasises the point that autonomic dysfunction may be a presymptomatic. Reliance on clinical impressions only may be misleading, and this might explain earlier notions of rarity of autonomic dysfunction in PD.

The only clinical variables that showed a relationship with autonomic dysfunction in PD were age at onset of PD and present age. It may well be that there is an additive effect of age on accelerated autonomic nervous system degeneration in PD. It is unlikely that advancing age alone will account for these changes in autonomic function because the age matched controls did not exhibit dysfunction anywhere as close as that demonstrated by the patients with PD. The summation of apoptosis and pathologic degeneration from PD appears a more plausible mechanism.

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