

## Impact of Handedness and Symptom Lateralization on Disease Characteristics in Parkinson's Disease in Calabar, Southern Nigeria

Sidney K. Oparah and Simon I. Ozomma

Department of Internal Medicine, University of Calabar Teaching Hospital, Nigeria

**Abstract:** *Background:* Laterality and lateralization of symptoms have been reported to influence disease characteristics in Parkinson's disease. Currently, none of the available Nigerian reports on Parkinson's disease explored the influence of these parameters on disease manifestations. *Method:* The study aimed to investigate the association between handedness and lateralization of motor symptoms and Parkinson's disease characteristics in a Nigerian city. Using a cross-sectional study design, we recruited Parkinson's disease patients at the University of Calabar Teaching Hospital in southern Nigeria from December 2016 to March 2020. A structured interviewer-administered questionnaire was used to obtain relevant information on demographic characteristics, handedness, the temporal profile and lateralization of Parkinson's disease symptoms in addition to other features of disease presentation. *Results:* The participants were forty-four patients comprising 27 males and 17 females with mean ages (SD) of 64 (12.49) and 68.3 (9.85) years, respectively ( $p=0.233$ ). 41 of them were right-handed, whereas 3 were left-handed. Left-handedness was associated with a younger age at onset ( $p=0.005$ ). The dominant side was affected at the onset in 34 of the patients ( $p<0.001$ ) and mainly affected a presentation in 35 of them ( $p<0.001$ ). REM sleep behavior disorder was more common at presentation with the dominant side predominantly affected ( $p=0.029$ ). *Conclusion:* Irrespective of laterality of body-side dominance, the dominant side of the body is often affected by Parkinson's disease at onset and remains predominantly affected in the course of the disease. REM sleep behavior disorder is more common when symptoms are predominant in the dominant limbs.

**Key words:** Parkinson's Disease • Parkinsonism • Laterality • Handedness • Lateralization • Nigeria

### INTRODUCTION

Parkinson's disease (PD) is a degenerative neurological disorder associated with loss of dopaminergic neurons in the nigrostriatal pathway [1]. It is generally reported to be of low prevalence rates in sub-Saharan Africa [2, 3]. In Nigeria, an age-adjusted prevalence rate of 67 per 100, 000 persons beyond 39 years has been reported (2). It constituted around 80% of the reported cases of Parkinsonism in Nigeria [4, 5]. The dynamics of the global prevalence of PD are expected to affect the low prevalence observed in some regions, as PD is ranked among neurological disorders with the fastest increments in prevalence, disability and mortality. The number of affected persons was estimated to have increased by more than double over the last three decades [6].

The motor manifestations include resting tremor, bradykinesia, rigidity and problems with balance; collectively referred to as the cardinal features of the disorder (7). Usually, there is an asymmetry with initial involvement of one side of the body which tends to remain worse throughout the disease, promoting reports of possible lateralized involvement of the nigrostriatal motor circuit [7, 8].

Handedness has been associated with the initial side of the body affected by the symptoms of PD; with the observation that the dominant side is usually the first to be affected, in both right-handed and left-handed persons [9, 10]. Furthermore, studies show some relationship between the side of the body affected at onset of PD and clinical characteristics of the disease manifestation; especially the course of disease progression, with the right-sided onset reported to be associated with faster

progression [11]. Some have reported an association between the side of initial motor manifestation and the pattern of cognitive impairment in PD [12, 13]. However, the suggested link between cognitive symptoms and initial side of the body affected by PD was not demonstrated by some studies that evaluated newly diagnosed cases and adduced the opinion that side of motor onset in the disease does not influence cognition, at least, at the early untreated stages of the disease [14, 15].

There are available albeit few reports on the clinical profile of Parkinson's disease in Nigeria [2-5]. However, none of the existing data on the clinical characteristics of Nigerians with PD explored the role of handedness and laterality of limb involvement in the disease features. Considering the debates surrounding the reported association between handedness and the initial side of limb involvement, with the nature and course of symptom manifestations in PD, we set out to investigate whether there is an association between handedness and the lateralization of motor symptom manifestations and the impact on clinical characteristics among patients diagnosed with Parkinson's disease at a tertiary health facility in the city of Calabar, Nigeria. To the best of our knowledge, this would be the first study to explore such aspects of Parkinson's disease presentations in Nigeria and the entire West African region. The study hypothesis was that handedness and side of disease onset, is associated with disease characteristics in Parkinson's disease.

## MATERIALS AND METHODS

This cross-sectional descriptive study was carried out at the University of Calabar Teaching Hospital located in Calabar; a city recognized as a prominent tourist destination in southern Nigeria. The Teaching hospital is the sole federal government-owned multi-disciplinary tertiary health facility that offers neurology clinic services in the City.

**Study Population:** The participants were recruited as part of an on-going program to generate data on Parkinson's disease in the city of Calabar. The participants who met the eligibility criteria were serially recruited from patients who presented for the first time with PD at the hospital during the study period.

The inclusion criteria of the study were as follows:

- Adults age 18 years and above

- Patients diagnosed to have Parkinson's disease by a specialist physician
- Anti-Parkinson drug naïve cases that presented for the first time at the neurology clinic
- Those that gave informed written consent

Patients with parkinsonism that did not fit into the study definition of Parkinson's disease and those that did not give consent were excluded from the study.

**Data Collection:** The study was conducted over forty months; from December 2016 to March 2020. Information on the participants' demographic characteristics, handedness, the temporal profile and lateralization of PD symptoms in addition to other features of disease presentation were obtained by the investigators, using an interviewer-administered questionnaire. Subsequently, we conducted a physical examination of the neurological system on each of the participants. Short term memory assessment was used to identify if a participant had memory deficits.

**Definition of Terms:** The diagnosis of Parkinson's disease was made based on the following criteria: (1) Presentation with motor symptoms of Parkinsonism in the absence of atypical features. (2) A history of an asymmetric pattern of symptoms at the initial stage, coupled with no evidence of a secondary cause of Parkinsonism.

The Hoehn and Yahr staging was used to determine disease severity. The participants' self-reported handedness was used to determine their handedness.

**Data Management:** Version 22 of the Statistical Package for Social Sciences (SPSS) software was used for the data analysis. Means and standard deviation (SD), median and ranges were used for continuous variables and simple proportions used for categorized data. Student's t-test was used to compare numerical variables. Bivariate analysis was used to explore the association between variables. We used the most common motor and non-motor symptoms of PD, to explore the association of variables with motor and non-motor symptoms of PD, respectively. The level of significance was set at  $p < .05$ .

**Ethical Consideration:** Ethical approval for the study protocol was obtained from the Research and Ethics committee of the University of Calabar, Teaching Hospital. The study was conducted in compliance with the Helsinki declaration of 1975, as revised in 1983 and 2013.

## RESULTS

44 participants comprising 27 males and 17 females presented with motor features of Parkinson's disease; giving a male to female ratio of 1.6: 1. 80% of them had non-motor features of PD. 93% of the participants were right-handed whereas 7% were left-handed. The right side was affected at onset in 35 (80%) of the participants and 9 (20%) had the left side of their body affected at the onset. The upper limb was first affected in 98% of them, whereas 2% had their lower limb as the first limb to be involved. At the time of presentation, the features of Parkinsonism were predominantly on the right side in 82% of the participants, whereas 18% of them had more features on the left. Table1 shows further details of their characteristics.

There was no association between sex of the participants and side of the body affected at onset ( $p=0.688$ ); sex of the participants and side of the body predominantly affected at presentation ( $p=0.942$ ); sex of the participants and involvement of the dominant side at the onset of Parkinsonism ( $p = 0.920$ ); sex of the participants and predominant involvement of the dominant side at presentation ( $p = 0.714$ ).

The dominant side of the body was more affected at the onset of PD; seen in 34 (77%) of the participants ( $p = 0.000$ ). Similarly, the dominant side of the body had more features at presentation, as seen in 35 (80%) of the participants ( $p = 0.000$ ). The body-side predominantly affected by Parkinsonism, at the time of presentation, had a high level of agreement with the initial side of the body affected at onset ( $\kappa=0.93$ ,  $\chi^2=38$ ,  $p < 0.001$ ).

Table 1: Background characteristics of the participants

Parameter	Males (n = 27)	Females (n = 17)	Total (N = 44)	p-value
Mean age in years (SD)	64 (12.49)	68.3 (9.85)	65.6 (11.62)	0.233
Median age	64	70	68	
Age group (%)				
<45	1 (4)	1 (6)	2 (5)	
45 – 59	12 (44)	0 (0)	12 (27)	0.009
60 – 74	9 (33)	13 (77)	22 (50)	
>74	5 (19)	3 (18)	8 (18)	
Mean age at onset (SD)	60 (13.28)	66.2 (10.29)	62.4 (12.47)	0.105
Median age at onset	56	68	63.5	
Mean duration of illness (SD)	3.9 (4.28)	1.9 (0.95)	3.1 (3.51)	0.069
Median duration of illness	3	2	2	
Age of onset group (%)				
<45	2 (7)	1 (6)	3 (7)	
45 – 59	13 (48)	4 (24)	17 (39)	0.395
60 – 74	9 (33)	9 (53)	18 (41)	
>74	3 (11)	3 (18)	6 (14)	
Handedness (%)				
Right	24 (89)	17 (100)	41 (93)	
Left	3 (11)	0 (0)	3 (7)	0.155
Hoehn&Yahr stage (%)				
I	6 (22)	6 (35)	12 (27)	
II	19 (70)	10 (59)	29 (66)	0.638
III	2 (7)	1 (6)	3 (7)	
Non-motor Features (%)				
Present	22 (81)	13 (76)	35 (80)	
Absent	5 (19)	4 (24)	9 (20)	0.688

Table 2: Participants' Handedness matched with age and duration of motor symptoms

Variable	Handedness of participants		p-value
	Right handed	Left handed	
Mean age in years (SD)	66.4 (11.62)	54.7 (2.89)	0.090
Median age	70	53	
Mean age at onset (SD)	63.2 (12.57)	52.0 (3.46)	0.005
Median age at onset	64	50	
Mean duration of symptoms (SD)	3.2 (3.64)	2.7 (0.58)	0.819
Median duration of symptoms	2	3	
Mean time to contralateral Involvement (SD)	2.7 (3.7)	1.7 (0.58)	0.225
Median time to contralateral Involvement	1.6	2	

Table 3: Laterality of PD involvement at onset matched with age and durations of motor symptoms

Variable	Side of the body affected at the onset		p-value
	Dominant side	Non-dominant side	
Mean age in years (SD)	66.8 (11.25)	61.7 (12.60)	0.227
Median age	69	55.5	
Mean age at onset (SD)	63.7 (11.87)	58.1 (14.15)	0.220
Median age at onset	64	50	
Mean duration of symptoms (SD)	3.0 (3.86)	3.4 (2.07)	0.780
Median duration of symptoms	2	3	
Mean time to contralateral Involvement (SD)	2.2 (3.82)	3.1 (2.21)	0.542
Median time to contralateral Involvement	1.33	2.5	

Table 4: Laterality of PD involvement at presentation matched with age and durations of motor symptoms

Variable	Predominantly affected side at presentation		p-value
	Dominant side	Non-dominant side	
Mean age in years (SD)	67 (11.15)	60.3 (12.55)	0.126
Median age	70	55	
Mean age at onset (SD)	63.9 (11.77)	56.6 (14.09)	0.117
Median age at onset	64	50	
Mean duration of symptoms (SD)	3.0 (3.81)	3.6 (2.13)	0.684
Median duration of symptoms	2	3	
Mean time to contralateral Involvement (SD)	2.2 (3.74)	3.3 (2.31)	0.468
Median time to contralateral Involvement	1.42	3	

Table 5: Levels of significance (p-values) of association between laterality of PD involvement and Parkinson's disease features

Clinical features	Dominant body side affected at onset	Dominant body side predominantly affected at presentation
Hoehn and Yahr stages	0.467	0.571
Tremors	1.000	0.795
Rigidity	0.561	0.659
Bradykinesia	0.557	0.222
Postural instability	0.557	0.703
Hypomimia	*0.012	*0.034
Non motor features	0.968	0.883
REM sleep behavior disorder	0.092	*0.029
Constipation	0.817	0.504
Hypo/anosmia	0.118	0.143
Memory deficits	0.606	0.586

\* = more common in non-dominant side involvement

# = more common in dominant side involvement

Table 6: Levels of significance of the association of handedness and symptom lateralization with Parkinson's disease features

Clinical features	(p-values of association)		
	Handedness	Affected side at onset	Predominant side at presentation
Hoehn and Yahr stages	0.435	0.571	0.668
Tremors	1.000	1.000	1.000
Rigidity	1.000	0.659	0.771
Bradykinesia	0.551	0.703	0.300
Postural instability	1.000	0.647	0.473
Hypomimia	*0.018	*0.034	0.089
Non motor features	0.363	0.883	0.725
REM sleep behavior disorder	0.721	0.504	0.251
Constipation	0.721	0.401	0.710
Hypo/anosmia	0.587	0.143	0.174
Memory deficits	*0.045	0.181	0.214

\* = more common in left-handed patients

# = more common in left side involvement

The mean (SD) and median ages at onset for those whose right side was affected at onset were 63.1 (12.06) and 64 years, compared to the ages of 59.7 (14.38) and 56 years for those with left-sided onset ( $p = 0.470$ ). The mean (SD) and the median duration of PD symptoms for those with right-sided onset were 3.1 (3.80) years and 2 years, compared to the duration of 3.3 (2.24) and 3 years for those with left-sided onset ( $p = 0.843$ ). The mean (SD) and median duration from the onset to contralateral involvement of symptoms for those whose symptoms started on the right side of their body was 2.3 (3.73) and 1.5 years, compared to the duration of 3.1 (2.46) and 3 years for those with symptom onset on the left ( $p = 0.567$ ).

The mean (SD) and median ages at the time of clinic presentation for those whose symptoms were predominantly on the right side were 66.5 (11.37) and 69 years, compared to the ages of 61.9 (12.76) and 57 years for those whose symptoms predominantly affected the left side of their body at the time of presentation ( $p = 0.470$ ). The mean (SD) and the median duration of PD symptoms for those whose symptoms were predominantly on the right side of their body at presentation was 3 (11.37) and 2 years, compared to durations of 3.5 (2.33) and 3.5 years for those whose symptoms predominantly affected the left side at the time of presentation ( $p = 0.741$ ).

The mean (SD) and median duration from the onset to contralateral involvement of symptoms for those whose symptoms predominantly affected the right side of their body at the time of clinic presentation were 2.2 (3.65) and 1.5 years, compared to durations of 3.4 (2.61) and 3.4 years for those with a left-sided predominance of PD symptoms at the time of presentation ( $p = 0.486$ ). The relationship of the participants' handedness with the ages and durations of Parkinson's disease manifestations are as shown in Table 2. The relationship of the laterality of PD involvement at onset and at presentation, with the ages and durations of Parkinson's disease manifestations, are as shown in Table 3 and Table 4, respectively.

There was no association between the side of the body affected at onset and presence of cardinal motor features ( $p = 0.883$ ); side of the body affected at onset and presence of non-motor features ( $p = 0.883$ ); side of the body predominantly affected at presentation and presence of cardinal motor features (1.000); the side of the body predominantly affected at presentation and presence of non-motor features ( $p = 0.725$ ); handedness and presence of cardinal motor features ( $p = 1.000$ ); handedness and presence of non-motor features ( $p = 1.000$ ).

The statistical levels of significance of the association between laterality of PD involvement and the clinical characteristics of PD are shown in Table 5; whereas, those between Handedness and symptom lateralization with the clinical characteristics of PD are shown in Table 6.

## DISCUSSION

Parkinson's disease ranks as the most common movement disorder and affects more males than females as reflected in this study. The effects of oestrogen, the female sex hormone, could have influenced the lower proportion of females in our study; a pattern that corroborates reports indicating that men are twice at risk of developing PD than women [16]. The sex-related differences in the risk of developing PD is believed to be in part from its anti-inflammatory modulatory effects on neuroinflammation; an important aspect of the pathogenesis of PD [16]. This view on the effects of oestrogen is reinforced by our observation that almost all the women in our study were aged 60 years and above, compared to the men. However, women tend to have a faster progression and poorer rates of PD survival [16].

There were more right-handed participants; reflecting the known fact that right-handedness is much more common compared to left-handedness. It is estimated that right-handed persons constitute about 90% of the global population [17-19]. Handedness has multifactorial determinants, including genetic and environmental factors [20, 21]. It appears that mechanisms that influence left-right asymmetries in the body, such as ciliogenesis and nodal signaling, also affect the development of brain asymmetry outwardly manifesting as handedness [22].

Our study demonstrated that laterality of body-side dominance coincided with the lateralization of PD symptoms at onset and at the time of presentation, irrespective of handedness. This corroborates the prevailing view regarding handedness and PD symptom manifestations [23, 24]. Handedness has been associated with lateralization of PD symptoms and the onset of symptoms occurs more on the dominant side [25]. Some investigators had reported on the utility of the body-side dominance in predicting the side of onset of motor symptoms in PD [23, 24]. However, some controversy exists whether the dominant side is initially vulnerable in PD and the fitness of handedness in predicting side of PD lateralization. Stochl *et al.* held a contrary view regarding handedness and PD symptom

manifestations (26). They reported the failure of handedness in predicting side of onset of motor symptoms in PD, contrary to the more widely held view [23-26].

We found a presentation with prominent PD symptoms in the dominant body-side, to be associated with the presence of REM sleep behavior disorder (RBD). RBD is one of the major non-motor features of the disease known to predate a diagnosis of PD based on the manifestation of more obvious motor symptoms [27, 28]. Reports by the Sleep Innsbruck Barcelona (SINBAR) group indicate that right-handed persons with REM sleep behavior disorder manifest left hemispheric predominance of subclinical nigrostriatal dysfunction [29]. Most of our patients were right-handed with left hemispheric dominance [30]. Given the integral relationship between PD and RBD and our observation that RBD was more among those with symptom predominance in the dominant limbs; perhaps, symptom predominance on the non-dominant side suggests other variants of Parkinsonism.

In our study, left-handedness was associated with younger age at onset of PD, presence of memory deficit and presentation with hypomimia. Left-handed persons with early onset PD whose symptoms started on the left side have been reported to have higher rates of long ambulatory disease survival [31]. However, observations on the impact of handedness on illness duration and severity were constrained by the constitution of the participants skewed towards patients at the early stages of PD. None of them had PD beyond the 3rd stage of Hoehn and Yahr grading; probably, a consequence of hinging eligibility on first clinic presentations.

Cognitive impairment linked to the side of motor symptoms has been demonstrated [12, 32]. Two patterns of mild cognitive deficits in PD have been proposed: one is influenced by the release of dopamine in the prefrontal cortex and affects frontostriatal executive functions; whereas, the other, which has an increased risk of conversion to dementia, affects visuospatial and memory functions [32, 33]. However, some investigators did not observe laterality related differences in cognitive deficits among drug-naïve PD patients at the early stages of the disease [14].

In addition to its link with left-handedness, presence of hypomimia was associated with non-dominant body-side involvement at onset of PD and predominance of PD motor symptoms on the non-dominant side at the time of presentation. We are unable to readily proffer

explanations for this observation considering the absence of lateralization-related differences in other motor manifestations; bradykinesia inclusive. Howbeit, our comments on hypomimia as observed in the study are expressed subsequently.

The right upper limb was the identified body site of symptom onset in a majority of the participants, corroborating the view that asymmetric motor symptoms in an upper limb are the most common initial finding in Parkinson's disease [34]. This feature helps to distinguish Parkinson's disease from other causes of Parkinsonism such as vascular Parkinsonism in which the lower limbs tend to be affected more than upper limbs, with early bilateral involvement [35].

Besides being the more frequent side of PD onset, the symptoms remained predominant on the right side of the body in most of the patients at the time of presentation; corroborating documented temporal course of PD motor features [36-38]. The factors that determine the laterality of PD and its neurophysiological origin remain unclear. Studies have revealed the presence of asymmetry in sub-cortical function and structure in patients with PD [8, 39]. Chloe *et al.* observed diminished uptake of dopamine and a greater degree of degeneration in the putamen and substantianigra contralateral to the side of PD symptom manifestation compared to what they found in the same structures on the ipsilateral side [8].

We found no association between lateralization of Parkinsonism with the age at onset, age at presentation, development of motor symptoms, occurrence of non-motor features, duration of disease and severity of PD. The lack of association remained whether the symptom lateralization at the time of onset or at the time of presentation was considered. Lateralization of motor manifestation has been associated with some PD characteristics. Persons with right-sided PD are said to have faster progression of the disease compared to those with symptoms predominantly on the left [11]. Left-side predominant PD has been linked to longer periods of survival following diagnosis [31]. As already stated, the recruitment of patients at the early stages of PD precluded meaningful observations on the relationship between symptom lateralization and disease duration and severity.

Hypomimia was more common among those with left-sided onset in our study; despite the lack of lateralization-related difference in the occurrence of tremors and other cardinal motor symptoms. This suggests contributions from factors beyond motor symptom manifestation to the link between hypomimia

and left-sided laterality. Besides PD, psychosocial or psychiatric conditions are known causes of hypomimia [40, 41]. It has been demonstrated that left-side predominance of symptoms in PD is associated with depression and anxiety [42]. To stretch the point further; Goodman *et al.* had reported on higher rates of emotional and behavioral problems in left-handed persons [43].

**Limitations:** We recruited patients during their initial clinic presentations, precluding assessments of Parkinson's disease characteristics on a long term basis. Also, we used simple short term memory assessment to identify the presence of memory deficits; a more comprehensive cognition assessment tool would have been more objective and quantitative.

## CONCLUSION

This study showed that irrespective of the laterality of body-side dominance, the dominant side of the body is often the side affected by PD at onset and remains predominantly affected by PD symptoms later in the course of the disease. REM sleep behavior disorder was more common when PD symptoms are predominantly on the dominant limb than in the non-dominant side. Left-handedness was associated with younger age at onset of PD and more common presentations with hypomimia and forgetfulness. This study raises the need for further investigations on Parkinson's disease such as; the relationship between handedness and age of onset in PD; the role of other factors in hypomimia as a feature of PD, amongst others.

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