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Investigation of Factors Affecting the Side of the Disease Onset in Parkinson's Disease

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ABSTRACT

Introduction: Parkinson's disease (PD) is a progressive neurodegenerative disease that starts unilaterally in almost all cases and tends to emerge on the side of the dominant hand, but what we know about the cause of this lateralization is limited. Frequent use of the extremity and physical activity are argued to be protective from PD in preclinical and clinical studies. This study aimed to evaluate the effect of handedness and working in occupations that require continuous use of upper extremities on the disease onset-side.

Methods: We retrospectively collected 84 PD patients who applied to Koç University Neurology outpatient clinic between July 2016-October 2018. We analyzed the parameters of the side and region of disease onset, age of onset, number of drugs used for PD, hand preference, and patients' occupations.

Results: The median age of our study group was 61 (53–69). Thirty (36%) of the 84 patients were women. Seventy-nine patients (94%) were right-handed. Eighty-three (99%) had asymmetric onset. The disease started on the dominant hand side in 47 patients (57%) and on the non-dominant hand side in 36 (43%) patients. In our group with a median disease duration of four (2–7) years, the side with more severe complaints measured with the Unified Parkinson's Disease Evaluation Scale was consistent with the onset-side of the disease (p<0.001). In addition, the number of drugs used for PD and the scale score were higher in patients with longer disease duration (p=0.039, p=0.005). The number of drugs used for PD was also higher in patients with lower extremity-onset or both upper and lower extremities affected simultaneously than the upper extremity-onset (p=0.005). While the probability of starting on the dominant side was 43% in patients working in occupations requiring continuous use of upper extremities, it was 65% in others (p=0.027).

Conclusion: According to this study, the onset of PD tends to be on the dominant hand side. Continuous upper extremity use may reduce the possibility of starting on the dominant side.

Keywords: Exercise, functional laterality, handedness, onset side, Parkinson's disease

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INTRODUCTION

Parkinson's disease (PD) is a progressive disease that significantly affects the quality of life (1). It is the most common neurodegenerative movement disorder with 0.3% prevalence in industrialized societies (2). The disease is pathologically characterized by the loss of dopaminergic neurons in the substantia nigra (SN) region of the brain. Most common neurological symptoms of PD at the time of onset are bradykinesia/akinesia, rigidity, resting tremor, and postural instability (1). The disease usually starts unilaterally. Moreover, the heavily affected side remains unchanged throughout the disease course. However, our knowledge about the underlying mechanisms of this persistent lateralization is limited (3).

The dopaminergic brain imaging studies and post-mortem histopathological examinations in patients diagnosed with PD showed that the brain hemisphere contralateral to the PD onset and the side that shows more disabling neurological symptoms during the disease course are more severely affected than the other hemisphere (4,5). However, no explanation has yet been found about the reason for this asymmetrical susceptibility.

Highlights

- **Parkinson's Disease (PD) tends to emerge at the dominant hand side.**
- **Working in jobs that require continuous upper extremity use has decreased this tendency.**
- **Occupational compulsory motor behaviors maintained throughout life may affect the onset side of PD.**

The human brain is naturally asymmetrical, and imaging studies have documented that it contains a higher number and more complex connections in the dominant hemisphere (6). In parallel, humans generally prefer one hand, the right hand, in 90% of cases (7). The relationship of this natural asymmetry with the PD onset side has caught the attention of many researchers. Studies so far have not reached

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a consensus on whether the PD onset side is more likely to be on the dominant hand side. This likelihood has been supported (8–10) and not supported (11,12) in the literature with previous studies.

An interesting result was reported in an animal study that unilateral PD model was conducted with 6-hydroxydopamine (6-OHDA). Forced use of the contralateral limb to the 6-OHDA induced dopaminergic deprivation decreases the intensity of the symptoms on that side (13). This case indicates that using the limb more intensively is protective against the effects of neurodegeneration (even though the pathological impact is more intense on that side). In parallel, studies support that exercise may have protective and alleviating effects in patients with PD (14). In addition, a study based on patients' self-reports on the frequency of physical activity that they do, claimed that the age of onset could be delayed by exercise (15). However, no previous studies have examined the possible effects of physical activity on the onset side of PD.

This study investigated the relationship between PD onset side and hand preference. We retrospectively scanned the data of PD patients followed up in our hospital and examined whether the disease started on the dominant hand side and working in occupations requiring continuous use of upper extremities (CUUE) affected the onset side of the disease.

METHODS

Our study was carried out by retrospectively scanning the files of patients who applied to the Koç University Neurology Department outpatient clinic between July 2016 and October 2018 and were followed up with the diagnosis of Parkinson's Disease. Patient records were scanned by one of our researchers (ÖÖÇ), all patients with PD were identified, and a number was assigned to each file. All 84 patients who applied during this period were included in the study. Another researcher (CMŞ) analyzed the patients' demographic data, and these numbers were transferred to a list without any other markers identifying the patients. Occupations were divided into two categories as those with continuous upper extremity use and those without. The Unified PD Rating Scale (UPDRS) score was reported as the mathematical sum of 42 questions and the scale's sections I, II, III and IV were also calculated separately. The number of drugs used for PD was found by adding up dopaminergic agents and as well as all medications used for symptomatic treatment. In addition, the equivalent dose of L-dopa was calculated for each patient according to current recommendations and included in the analyzes (16). Statistical analyses were performed by a blinded investigator (EÖ) on this final list. The Koç University Clinical Research Ethics Committee approved this study with the decision number 2021.319.IRB1.145.

All statistical analyses were performed using IBM SPSS 28.0 (IBM Corp., Armonk, NY, USA) software. Normal distribution was tested with the Shapiro-Wilk test. Categorical variables are shown as percentages and continuous variables as median (interquartile range). Mann-Whitney U or Kruskal-Wallis tests were used for numerical differences between groups. Chi-square test, Pearson chi-square test, or Fisher exact test were used for categorical variables. A $p<0.05$ value was accepted for the two-way analysis to be statistically significant.

RESULTS

In our study, the initial symptoms were asymmetrical in 83 (99%) out of 84 patients. Our study group was divided into two groups in one of which the disease started on the dominant hand side of the patient and in the other, the disease started on the non-dominant hand side, within the framework of our primary endpoint. There was no statistical significance between our study groups according to age, sex, hand preference, number of drugs used for PD, comorbidities, family history of PD, age at onset of disease, disease duration, disease onset region, UPDRS score, and having an occupation that requires CUUE. In the neurological examination, the side with more severe symptoms was found to be significantly compatible with the onset side ($p<0.001$). The demographic characteristics of our study are summarized in Table 1.

Thirty (36%) of the 84 patients who participated in our study were women. Seventy-nine patients (94%) were right-handed. The median age of our study group was 61 (53–69). Female participants in our study were younger than males ($p=0.015$). The median age was 58 (51–65) for women and 63 (55.75–70) for men. There was no significant difference between the age of onset of the disease ($p=0.058$). Only 4 (5%) of 29 (35%) patients working in jobs requiring continuous use of upper extremities were women, and this rate was significantly lower than men ($p=0.002$).

The first symptoms of 44 (56%) right-handed patients in our group started on the right and 34 (44%) on the left. Three (60%) of the left-handed patients had their first signs of PD on the left and 2 (40%) on the right. When the relationship between hand preference and the starting side was examined, the odds ratio (odds ratio-OR) was 1.9 (95% confidence

Table 1. Demographic characteristics of the patients

	Disease onset side		
	Dominant (n=47)	**Non-dominant (n=36)**	**P-value**
Age	63 (53-70)	59 (52-67)	0.246
Female sex	15 (32%)	15 (42%)	0.359
Right-handedness	44 (94%)	34 (94%)	1.000
PD drugs (how many)	3 (2-3)	2 (2-3)	0.250
L-dopa ED (mg)	599 (475-1165)	533 (400-862)	0.293
Comorbidity	35 (75%)	28 (78%)	0.727
Family History of PD	6 (13%)	7 (20%)	0.407
Age at Onset	58 (48-64)	56 (46-62)	0.331
Disease Duration (years)	4 (2-8)	5 (2-7)	0.796
Onset Region (upper ext.)	32 (70%)	24 (75%)	0.600
Occupation with CUUE UPDRS III right>left Total UPDRS Score	13 (28% 37 (90%) 32 (25-43)	17 (49%) 4 (13%) 35 (25-45)	0.052 **<0.001*** 0.452

CUUE: Continuous use of upper extremities; ED: Equivalent dose; Ext: Extremity, PD: Parkinson's disease; UPDRS: Unified PD rating scale.
* p-value is significant.

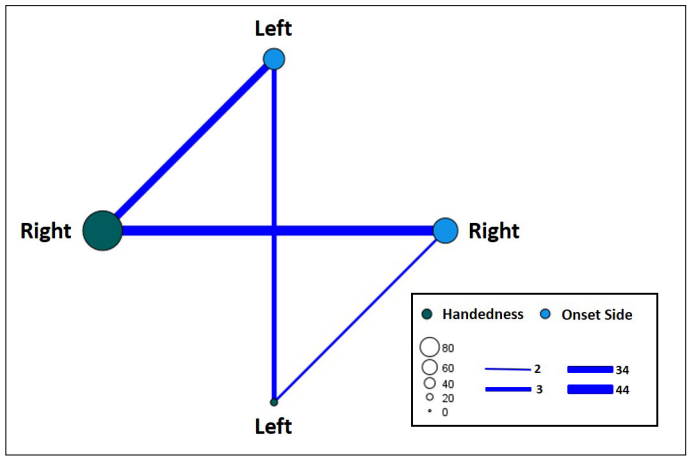

Figure 1. Map showing the relationship between hand preference and PD onset side. The green circles indicate the number of right-handed or left-handed patients, and the blue circles the onset side of the disease. The size of the circles and the numbers corresponding to the thickness of the connecting lines are summarized in the figure legend.

interval 0.3–12.3) (p=0.652). The relationship map between hand preference and the starting side is shown in Figure 1. The disease started on the dominant hand side in 47 patients (57%) and on the non-dominant hand side in 36 (43%) patients. The baseline did not differ significantly in the dominant and non-dominant hemispheres (p=0.227). The disease started on the dominant side in 13 (43%) of 30 patients working in jobs requiring continuous use of upper extremities. In this group, there was no significant difference between those whose first symptoms started on the dominant side and those whose did not (p=0.465). In 52 patients working in jobs that do not require continuous use of upper extremities, the dominant side onset was 34 (65%). This value was significantly higher than those with non-dominant side onset (p=0.027).

The median disease duration was four years (2–7). When the data are analyzed by dividing them into two groups as patients with a disease duration of <4 and ≥4 years, as would be expected, as the duration of disease increases, the number of PD drugs used and the calculated L-dopa equivalent dose were significantly higher (p=0.039, p=0.011, respectively). In addition, the total UPDRS score and, when analyzed separately, the total score of the UPDRS-II, UPDRS-III, and UPDRS-IV sections were found to be higher in patients with longer disease duration (p=0.005, p=0.020, p=0.0041, p=0.002, respectively).

Parkinson's disease started on the upper extremity in 56 (72%) patients, on the lower extremity in 12 (15%), and 10 (13%) patients experienced first symptoms simultaneously in both lower and upper extremities. The number of drugs used for PD differs significantly according to the disease onset site (p=0.005). Upper extremity onset predominantly detected in our group and is also common in the literature, is associated with less drug use. In pairwise comparisons, patients with upper extremity onset were found to use significantly fewer PD drugs than those with lower extremity onset and those with upper and lower extremity onset simultaneously (p=0.006 and p=0.034, respectively). However, there was no correlation between the disease onset site and the L-dopa equivalent dose of the dopaminergic drugs used by the patients (p=0.072).

Thirteen patients (16%) in our study had a family history of PD. In our study group, whose median age was 64, one or more comorbid diseases was detected in 64 patients (76%). Patients with comorbidity were significantly older than those who did not have a comorbidity, as expected (p=0.047).

DISCUSSION

Parkinson's disease often has a unilateral onset and is of great importance in the clinical differential diagnosis of this disease as one of the main diagnostic criteria. However, the reason for this lateralization remains a mystery. Our study evaluated the relation between disease onset side with handedness and the history of working in jobs requiring CUUE. The frequency of onset of the disease on the dominant hand side was higher. Hand preference and initial side tend to be parallel, but this hypothesis could not be supported statistically. It has been shown that the frequency of onset of the disease on the dominant side increases in those who do not use the upper extremity continuously. These results can be interpreted as the continuous use of the upper extremity, assuming that the dominant side must have been used and stimulated more, decreasing the likelihood of initiating symptoms on the same side.

Although the onset on the dominant hand side has been reported higher than the non-dominant onset in PD patients, the hypothesis that PD starts on the dominant side has been supported by some but not all of the previous studies (8,10–12). Among these reports, a meta-analysis from 2012 that included 4405 asymmetric PD patients from 10 different studies has concluded that in right-handed patients, onset on the right was found to be 59%, and onset on the left was found to be 41%. In left-handed patients, onset was 59% on the left and 41% on the right (OR 2.13 (95% CI, 1.71-2.66)) (9). These rates are consistent with the rates were found in our study. The inability to reach statistical significance in our study and formers can be attributed to the small number of patients, especially the low number of left-handed patients. When the reports on this subject have been examined so far, it should be noted that although some studies could not prove a higher probability of dominant side onset, there is no support in favor of the beginning on the non-dominant side.

Imaging studies and post-mortem examinations have shown that the contralateral hemisphere of the extremity, which has more severe neurological findings in PD, is more severely affected (4,5). However, the question is why there is a more severe loss of dopaminergic neurons on that side initially. It cannot yet be explained how genetic and environmental factors and age, which are currently considered among the most critical risk factors for PD, cause asymmetric loss (17). The literature's suggested explanations for this asymmetrical susceptibility can be evaluated under three main headings (3). One of the theories is that the SN reserve is unequal at birth. Hence, the dopaminergic loss in the vulnerable side reaches the threshold to be symptomatic earlier than the other side. Thus, this could explain why the results are inconsistent, although solid studies have shown that hand preference predicts the onset side (18). A second view is that the damage caused by increased metabolic demand and oxidative stress in the dominant hemisphere makes the dominant hand more sensitive (19). However, studies pointing to the protective role of exercise in PD (14) and the fact that exercise has a place even in our clinical practice reduce this possibility. The third view, which is related to the importance of exercise, is that unlike the second, the dominant hemisphere should be protected due to more frequent stimulation. In parallel, animal studies have proved that the forced-used of the extremity contralateral to the PD-induced hemisphere reduces PD-related neurological deficits (13). In our study, the decrease in the frequency of disease onset on the dominant side in patients who did not frequently use their upper extremities compared to the whole sample was interpreted in favor of the neuroprotection hypothesis.

Among the other results of our study, the persistence of the onset side of PD as the side with more severe findings in the neurological examination is a well-known observation in PD. In addition, we demonstrated the number of drugs used for PD, the total L-dopa equivalent dose of drugs, and the severity of the findings measured by the UPDRS score were higher in patients with longer disease duration, as expected.

We detected upper extremity onset more frequently among PD patients. This is again in agreement with the literature (20). Interestingly, in our study, it was found that patients with upper extremity onset took fewer PD drugs than those with lower extremity or both upper and lower extremity onset, regardless of disease duration. Although a direct relationship between the site of onset and the severity of the disease has not been reported, the frequency of dyskinesia and non-motor symptoms is higher, especially in PD subtypes with impaired gait and balance (21). Therefore, it can be assumed that the number of drugs prescribed for the broad spectrum of symptoms can be increased in patients with lower extremity involvement.

Our study has significant limitations. First of all, our study is a retrospective study, our sample size is small, and the initial side of the disease is based on patients' recollections. However, in our study, the disease onset side and the side with more severe findings in the neurological examination were compatible. Since the initial side in PD often remains the side with more severe signs throughout the disease progression (5), this can be interpreted as the patients remembering correctly. Secondly, the patients were dichotomized as those who work in jobs that require continuous use of upper extremities and others, but this is not based on a structured inquiry. In future studies, detailed documentation should be made by collecting the answers to the questions like how many hours a day the patients actively use their hands, which hand they use, and what kind of movements they make.

CONCLUSION

Parkinson's disease is a progressive disease that limits the quality of life. Current researches and discussions continue about the triggering causes of this disease with well-defined pathological features. The factors affecting the starting side have not been clarified yet. In this study, we showed that in addition to the tendency of the starting side to be compatible with hand preference, a lifestyle that requires constant physical movement may have a protective effect on the dominant hand side. We think that these data can broaden our perspective to reveal the pathophysiology of the disease and eventually management strategies.

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Ethics Committee Approval: Our study was approved by the Koç University Clinical Research Ethics Committee with the decision number 2021.319.IRB1.145.

Informed Consent: Written informed consent was not taken from participants. Our ethical committee waived the requirement.

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Conflict of Interest: There is no conflict of interest in our study.

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