Sabuncuoglu Serefeddin Health Sciences (SSHS)

ISSN: 2667-6338, 2021/Vol.3:3/63-88

THE ASSOCIATION WITH THE AUTONOMIC NERVOUS SYSTEM FINDINGS AND PREDOMINANT SIDE OF ONSET OF IDIOPATIC PARKINSON'S DISEASE

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Research Article

Received: 06/11/2021; Accepted: 25/12/2021

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Abstract

Idiopathic Parkinson's Disease (iPD) is a neurodegenerative disorder which the motor and nonmotor symptoms are accompanied with. Non-motor features can be seen in every stage and can appear before motor findings arise. Autonomic dysfunction is one of the most prevalent non-motor features of iPD which includes enteric and bladder dysfunction, sexual dysfunction, sweating disorders, orthostatic hypotension. Not only because they seem very often but since they affect the quality of life of the patients, non-motor symptoms have great importance. The asymmetry of brain as a universal phenomenon describes the function of the whole nervous system. This asymmetric involvement is also manifested in iPD studies clinically and neuropathologically. In this study we examined 30 İPD patients to investigate the association of asymmetry in iPD and autonomic nervous system involvement. Patients are gone through a detailed physical and neurological examination. H&Y, UPDRS, MMT scores are enrolled. Autonomic symptoms are quest ionized with 12 items. When the outcomes are examined, we saw that autonomic disorder severity increases with the term of disease as well as the severity of motor symptoms. Furthermore, we came through that the autonomic symptoms can be seen from the early stages of the disease. The patients without bradykinesia had better responses to the therapy. The frequency of hallucination increased with the age and the severity of the disease. When the association with the side of onset of İPH symptoms and the autonomic involvement

examined, which was the aim of this study, there was not a significant association but a week correlation.

Key Words: Parkinson's disease, Autonomic nervous system, Asymmetric involvement

Özet

iPH motor ve non-motor semptomların eşlik ettiği nörodejeneratif bir bozukluktur. Non-motor özellikler her evrede görülebilir ve motor bulgulardan daha önce ortaya çıkabilir. Otonomik disfonksiyon iPH'nin en yaygın non-motor özelliklerinden biri olup bağırsak ve mesane disfonksiyonu, seksüel disfonksiyon, terleme bozuklukları, ortostatik hipotansiyon gibi bulguları içerir. Non-motor semptomların önemi sadece çok sık görülmesinde değil, aynı zamanda hastanın yaşam kalitesi üzerinde büyük bir etkisinin olmasında yatar. Beynin asimetrisi, tüm sinir sisteminin fonksiyonunu tanımlayan evrensel bir olgu olarak karşımıza çıkmaktadır. iPH çalışmalarında da bu asimetrik tutulum hem klinik hem de nöropatolojik olarak ortaya konulmuştur. Çalışmamızda da iPH'daki asimetri ile otonom sinir sistemi tutulumu arasındaki ilişkiyi incelemek için 30 iPH hastası ile çalışıldı. Hastalar ayrıntılı fizik ve nörolojik muayeneden geçirildi. H&Y, UPDRS, MMT skorları alındı. Otonom bulgular 12 maddede sorgulandı. Sonuçlar incelendiğinde hastaların hastalık süresi arttıkça motor bulguların şiddetinin arttığı gibi otonom tutululm şiddetinin de arttığı belirlendi. Ayrıca otonom bulguların hastalığın ilk dönemlerinden itibaren görülebileceği sonucuna ulaşıldı. Bradikinezi olmayan hastaların tedaviye daha iyi yanıt verdiği ortaya konuldu. Hastaların yaş ve hastalık şiddeti arttıkça halüsinasyon görülme sıklığının arttığı görüldü. Çalışmamızın amacı olan dominant tutulan taraf ve otonom tutulum ilişkisi incelendiğinde ise aralarında anlamlı derecede bir ilişki saptanmadı ancak çok zayıf bir korelasyon bulundu.

Anahtar Kelimeler: Parkinson hastalığı, Otonomik sinir sistemi, Asimetrik tutulum

1. Introduction

Idiopathic Parkinson's Disease (IPD) is an age-related, neurodegenerative disease (Ropper et al., 2006, Jankovich et al., 2008). It is known that this disease, of which onset and progression are typically gradual, often begins asymmetrically. Resting tremor, bradykinesia, rigidity (positive phenomena), loss of postural reflex, flexion posture, and freezing (negative phenomena) are considered as motor symptoms (Fahn & Przedborski, 2008). As a rule, these symptoms start insidiously and progress slowly, and over time the disease passes to the other half of the body (Jankovich et al., Fahn & Przedborski, 2008, Fahn & Przedborski, 2008). In addition to these findings, autonomic symptoms may be observed depending on the degeneration of spinal autonomic neurons or the side effects of the drugs used in the treatment, especially in the advanced stages of the disease (Iodice et al., 2011, Mehndiratta et al., 2011). Autonomic symptoms considered within nonmotor symptoms include constipation, frequent urination and urgency, impotence, sweating disorder, drooling, and orthostatic hypotension (Visser et al., 2004, Tolosa et al., 2008). Motor symptoms begin asymmetrically and in later stages, one side of the body shows more distinct symptoms than the other side, and such an asymmetric involvement is not expected in autonomic and non-motor symptoms.

Although the prevalence of non-motor symptoms and their negative effects on the quality of life create an increasing awareness, they are not yet adequately diagnosed and untreated. The approach to IPD requires a better understanding of both motor and non-motor symptoms, the relationship between these symptoms and how they respond to treatment methods (Lyons & Pahwa, 2011). Pathological and clinical studies have shown that non-motor symptoms occur earlier. As stated in the recent publications of the American Academy of Neurology on the treatment approaches of non-motor symptoms, it affects the quality of life more than motor symptoms (Zesiewicz et al., 2010).

The neuropathology underlying the IPD also involves parts that are not directly related to motor control such as the locus coeruleus, dorsal nucleus of the vagus, brainstem raphe nuclei, hypothalamus, bulbus olfactory, limbic cortex and most of the neocortex (Braak et al., 2003).

Autonomic symptoms in IPD are not specific for the disease (Micieli et al., 2003). However, symptoms of autonomic nervous system (OSS) dysfunction are observed in 90% of cases with IPD (Gurevich & Korczyn, 2005). IPD primarily affects the brain, but it is known that changes in central and peripheral postganglionic autonomic nerves also play a role in the pathophysiology of autonomic symptoms (Micieli et al., 2003, Gurevich & Korczyn, 2005, Sethi, 2008). Central autonomic nuclei such as sympathetic ganglion neurons and parasympathetic myenteric and

cardiac plexuses, hypothalamus, and dorsal motor nucleus of the vagus nerve show Lewy body degeneration (Fahn & Przedborski, 2008, Akyüz,2003). Autonomic disorders in patients with IPD occur due to degeneration of cholinergic, monoaminergic, and serotoninergic nuclei and dopaminergic treatment (Gurevich & Korczyn, 2005).

In most cases, asymmetric involvement in clinical symptoms is observed from the onset of the disease, but the mechanism of this side selection is not fully understood. Also, lateral involvement is not limited to motor symptoms (Djaldetti & Ziv, 2006).

In some studies, indicating asymmetry in autonomic functions, plantar sympathetic skin responses (SSR) were measured together with control groups, and an asymmetric involvement with abnormal patterns in the dominant affected side was detected in early-stage patients.

In a study conducted by Schestatsky et al. in 2006, the SDR amplitude was found to be significantly lower in the upper and lower extremities in patients with IPD compared to the control group (Schestatsky et al., 2006).

In another study conducted in 2009, language functions of middle-stage IPDs were examined, and it was shown that those with dominant left-sided motor symptoms had regression in their language functions including complex expressions regardless of the severity of the disease (Holtgraves et al., 2010).

In this study, the relationship between the dominant affected side and the presence and severity of autonomic involvement in IPD was investigated.

1.1. The predominant party and disease severity in IPD

Early motor symptoms in IPD typically start in one half of the body. Unilateral involvement with or without axial involvement is essential in defining early-stage disease (Hughes et al., 1993, Hoehn & Yahr, 1968, Gelb et al., 1999). It is a known fact that the motor symptoms of IPD mainly arise from the progressive asymmetric result in nigral dopaminergic neurons. However, this side involvement in IPD seems to be not specific to motor symptoms only. For example, it was observed that the complaints of IPD patients who often complain of pain and fatigue and who have autonomic symptoms even in the early stages may be more dominant on the affected side (Djaldetti et al., 2006, Friedman et al., 2001, Djaldetti et al., 2001). Patients with left side involvement predominantly show right hemisphere pathology, those with right side involvement show left hemisphere pathology (Kempster et al., 1989).

Motor symptoms in IPD do not occur without a loss of around 80% in striatal dopamine and 50% in nigral neurons (Kempster et al., 1989, Agid et al., 1989, Marsden, 1990). Even in a healthy brain, there is less dopamine in the right-sided striatum, and this does not cause disease, suggesting that the left hemisphere is more sensitive to large amounts of dopamine losses than the right hemisphere (Haaxma et al., 2010). This side involvement effect has been confirmed in independent pathology (Kempster et al., 1989, Agid et al., 1989) and neuroimaging studies (Djaldetti et al., 2006, Dethy et al., 1998, Djaldetti et al., 2009, Djaldetti et al., 2011, Morrish et al., 1995). In a limited number of studies, the relationship between non-motor symptoms and parkinsonism involvement has been investigated, but it can be said that right-sided IPDs progress worse than left-sided involvement, according to available data (Cubo et al., 2010). In terms of motor deficit, it has been reported that IPD patients with right-sided involvement tend to be worse in neuropsychological tests showing dominant hemisphere functions than those with left involvement, and their cognitive scores measured by MMT tend to be lower (Cooper et al., 2009).

In a study published in 2013, patients who had been diagnosed with IPD for more than 20 years but did not progress beyond the H&Y stage 4 and continued their mobility were the subjects, and in these patients, left-handedness and motor findings were significantly higher in left-handedness and motor findings compared to the control group (Martinez-Martin et al., 2007).

In the Cubo study (Cubo et al., 2012) conducted in 2012, clinical correlations of apathy in IPD were investigated and it was observed that IPD patients with right sided involvement showed more left hemisphere pathology and the rate of apathy development was higher. Besides, in neuroimaging studies on apathy in IPD, it has been shown that bias involvement shows a strong relationship with the presence and severity of apathy in IPD (Liotti & Mayberg., 2001). In a pilot study conducted in 2010, the phenomenology of pain and the effect of mood disorders and their relationship with hemispheric asymmetry at the onset of the disease were studied in IPD. According to the results of this study, an excellent correlation was found between pain and mood in patients with left-sided IPD. And it was determined that patients with left-sided involvement with mood disorders are more sensitive to pain, and that there is no such relationship between pain and mood in patients with right-sided involvement (Mc. Namara et al., 2010).

2. Material and method

This study was conducted with the approval of Abant İzzet Baysal University Faculty of Medicine (AİBÜTF) Medical Ethics Committee with No 2013/70. In the study, among the patients

who applied to AİBÜTF Neurology Department Clinic between 5-11 months of 2013, patients who were diagnosed with IPD according to BKPDBB clinical criteria were evaluated and 30 patients, 20 male and 10 female, were included in the study. All individuals participating in the study were informed about the purpose of the study and the tests to be applied and their approval was obtained.

Detailed physical and neurological examinations of all individuals included in the study were performed. Demographic characteristics of the patients such as age, gender, and profession were recorded. In addition, the presence of systemic diseases such as hypertension (HT), congestive heart failure (CHF), coronary artery disease (CAD), diabetes mellitus (DM), cerebrovascular accident (CVA) was questioned in their personal and family history. The dominant affected side, disease drug response, and family history of IPD were evaluated. Detailed anamnesis of the patients was taken and the age of onset of the disease, duration of the disease, prominent complaints, and the drugs used were questioned. For autonomic symptoms, sweating, oily skin, hair loss, leg oedema, constipation, dysphagia, orthostatic hypotension, frequent urination, urinary urgency, nocturia, incontinence, impotence was questioned. The time of onset of these symptoms was determined. Arterial blood pressures were measured in suitable individuals while lying, sitting and standing to detect orthostatic hypotension. A decrease in systolic 20 mmHg or more and/or diastolic 10 mmHg or more in lying-sitting and lying-standing was accepted as orthostatic hypotension. The presence of hallucinations was questioned. The severity of the disease was determined with the Unified Parkinson's Disease Rating Scale (UPDRS).

The staging of the disease was made with the H&Y scale. MMT was applied. The questions are as far away from medical language as possible and simplified in a way that patients can understand.

3. Statistical Analysis

The data were analysed using descriptive statistics, independent student T test, Mann Whitney U test, Pearson and Spearman's Rho correlation tests in SPSS 20 package program. Data presentation was made using number, percentage values, mean, standard deviation, standard error mean, minimum-maximum values.

4. Results

A total of 30 patients between the ages of 50-83 (mean 68.8±8.6 years) were included in our study. 20 of the patients were male (66.6%), 10 of them were female. The mean age of men was 70.9±8.2 and the mean age of women was 64.8±8.3.

The mean duration of the disease was found as 59.9±47.3 months. The mean UPDRS values of the patients were 30.1±17 and the mean MMT values were 26.3±3.4 points. Disease severity of IPD was found to be the most frequent stage 1.5 according to H&Y staging. Hallucination was detected in 36.6% of the patients (mean: 1.37). The mean time of onset of autonomic findings (months) was 61.4±54.9. When a total of 12 autonomous signs were scored, the mean value was found to be 5.2±2.3.

IPD started from the right side in 19 (63.3%) of 30 patients, and from the left side in 11 (36.6%). When the autonomous total score and the dominant side were compared, no significant results were found in parametric and nonparametric tests (p>0.005, Spearman c: 0,27, Pearson c: 0,22) (Table 1).

Table 1. Relationship of dominant affected sides and autonomic involvement

	Right side	**Left side**
Distribution/Kolmogorov Smirnov	p: 0.643 N: 19	p: 0.809 N: 11
Autonomic involvement mean score	4,8±2.3	5.9±2.1
Student T test	p: 0.224	

When each autonomic findings were compared separately, there was no significant result. The duration of the disease was found to be significantly correlated with leg edema (p: 0,005, c: 0,35), weakly correlated with constipation (p: 0,019, c: significantly correlated with frequent urination (p: 0,003, c: and significantly correlated with urinary urgency (p: 0.019, c: 0.42). 0,019, c: 0,42). No significant correlation was found between other autonomic findings and the duration of the disease. A significant correlation was found between the total autonomous score and the duration of the disease (According to Spearman's rho analysis, p: 0.01, c. 0.46, according to Pearson analysis p: 0.01, c: 0,43). When H&Y and autonomic findings were compared, no significant relationship was found between individual or total scores and H&Y stages (p: 0,09, c:0,31). Although there was no significant correlation between UPDRS and total autonomic score, there

was a slight correlation (p: 0,07, c: 0,337). No significant relationship was found between MMT and autonomic findings (p:0.53, c: 0,12). A significant negative correlation was found between disease drug response and autonomic findings (p: 0,01, c: -0,43). No relationship was found between other autonomic findings and drug response (Table 2).

The time spent since the onset of autonomic findings was compared with the IPD duration of the disease and the age of the patient for. There was no correlation between age and autonomic involvement duration (p: 0,25, c: 0,21).

Table 2. Autonomic findings, rates, presence of correlation

	Incidence and average	Duration of disease	HY	UPDRS	MMT	Dominant affected side	Drug response
Avg. Hypot.	33,3% 1,33	p:1,00 c:0,00	p:0,41 c:0,15	p:0,30 c:0,19	p:0,14 c:0,27	p:0,82 c:-0,04	p:0,96 c:0,00
Leg oedema	26,6% 1,27	p:0,05 c:0,35	p:0,52 c:0,12	p:0,80 c:0,04	p:0,40 c:0,15	p:0,25 c:0,21	p:1,00 c:0,00
Constipation	56,6% 1,57	p:0,02 c:0,42	p:0,55 c:0,11	p:0,15 c:0,26	p:0,71 c:0,07	p:0,42 c:0,15	p:0,10 c:0,30
Frequent urination	73,3% 1,73	p:0,00 c:0,52	p:0,34 c:0,18	p:0,17 c:0,25	p:0,78 c:-0,53	p:0,34 c:0,18	p:0,78 c:-0,05
Urinary urgency	70% 1,70	p:0,02 c:0,42	p:0,23 c:0,22	p:0,08 c:0,32	p:0,85 c:0,03	p:0,80 c:0,04	p:0,19 c:-0,24
Sweating	43,3% 1,43	p:0,30 c:0,19	p:0,29 c:0,19	p:0,24 c:0,22	p:0,80 c:0,04	p:0,43 c:0,14	p:0,14 c:-0,27
Oily skin	13,3% 1,13	p:0,63 c:0,09	p:0,26 c:0,21	p:0,14 c:0,27	p:0,74 c:-0,06	p:0,40 c:0,15	p:0,56 c:0,11
Dysphagia	20% 1,20	p:0,19 c:0,24	p:0,44 c:0,14	p:0,70 c:0,07	p:0,75 c:0,05	p:0,93 c:0,01	p:0,01 c:-0,43
Hair loss	16,6% 1,17	p:0,89 c:0,02	p:0,67 c:0,08	p:0,43 c:0,15	p:0,91 c:0,02	p:0,24 c:-0,22	p:0,76 c:0,05
Nocturia	70% 1,70	p:0,26 c:0,21	p:0,71 c:0,07	p:0,67 c:0,08	p:0,85 c:-0,03	p:0,65 c:0,08	p:0,59 c:
Incontinence	56,6% 1,57	p:0,72 c:-0,06	p:0,86 c:0,03	p:0,88 c:0,02	p:0,50 c:-0,12	p:0,28 c:-0,20	p: c:
Impotence	53,3% 1,43	p:0,49 c:0,13	p:0,23 c:0,22	p:0,41 c:0,15	p:0,44 c:0,14	p:0,42 c:-0,15	p:0,62 c:0,09
Autonomous score	5,2	p:0,01 c:0,46	p:0,09 c:0,31	p:0,07 c:0,33	p:0,12 c:0,53	p:0,76 c:-0,05	p:0,78 c:-0,05

Spearman's rho correlation analysis

There was a moderate-good, significant correlation between the duration of the disease and the duration of autonomic involvement (p: 0,00, c: 0.67) (Table 3).

Table 3. Correlation between time of onset of autonomic signs and duration of disease and age

	Duration of disease (month)	Age (month)

Autonomous onset (month)	p: 0.00 c: 0.67	p: 0.25 c: 0.21

As expected, there was a moderate to good positive correlation in correlation tests between disease duration and H&Y stages and UPDRS scores (Table 4). As expected, a negative correlation was found between H&Y and UPDRS scores and MMT scores (p: 0.04, c: -0.372, p: 0.011 between UPDRS and MMT, c: -0.457).

Table 4. Correlation between H&Y and UPDRS and disease duration

	H&Y		**UPDRS**	
	Spearman	**Pearson**	**Spearman**	**Pearson**
Duration of disease	p: 0.003 c: 0.52	p: 0.02 c: 0.42	p: 0.000 c: 0.616	p: 0.003 c: 0.525

In other words, as the disease stage increased, it was confirmed that there was an increase in MMT scores. No relationship was found between the duration of the disease and MMT (p: 0.542, c: -0.116) (Table 5).

Table 5. Correlation between H&Y, UPDRS, disease duration and MMT

	Duration of disease	**H&Y**	**UPDRS**
MMT	p: 0.542 c: -0.116	p: 0.031 c: -0.395	p: 0.015 c: -0.441

There was no relationship between the dominant affected side and the H&Y (p: 0,679, c: 0.07) and UPDRS (p: 0.413, c: 0.155) scores (Table 6).

Table 6. Correlation between the dominant affected side and H&Y and UPDRS.

	H&Y	**UPDRS**
Dominant affected side	p: 0.67 c: 0.07	p:0.413 c:0.155

Spearman's rho correlation analysis

The dominant affected side was compared with disease drug response (p: 0.34, c: -0.179), disease duration (p: 0.117, c: -0.253), H&Y phase (p: 0.241, c: -0.221), UPDRS (p: 0.318, c: -0.189). Disease drug response had no correlation with any of these (Table 7). There was a significant positive correlation between parkinsonian gait and H&Y (p: 0.001, c: 0.59), UPDRS (p: 0,001, c: 0,58), duration of disease (p: 0.001, c:0.58) and e negative 36 correlation with disease drug response (p: 0.02, c:-0.43), when compared with the clinical signs of IPD individually.

A positive correlation was found between H&Y and bradykinesia (p: 0.001, c: 0.55), UPDRS (p: 0.001, c: 0.58), duration of disease (p: 0.007, c:0.48) and a negative correlation with disease drug response (p: 0.03, c: -0.40). It was concluded that patients with characteristic Parkinson's gait and/or bradykinesia were less responsive to drug therapy. Among the findings, there was a significant correlation with rigidity and H&Y (p: 0.02, c: 0.41) and UPDRS (p: 0.01, c: 0.43) (Table 8).

Table 7. Correlation between drug response and dominant side, disease duration, H&Y, UPDRS

	Dominant side	**H&Y**	**UPDRS**	**Duration of disease**
Disease drug response	p: 0,343 c: -0,179	p: 0,242 c: -0,221	p: 0,318 c: -0,189	p: 0,117 c: -0,253

Spearman's rho correlation analysis

When the relationship between disease duration, age, H&Y, UPDRS, MMT and hallucinations was examined, there was a significant relationship between age and presence of hallucinations (p:0.038, c: 0,381). A significant relationship was also found between age and specifically visual hallucination (p: 0,03, c: 0,397).

Table 8. IPD findings, frequency, correlation, correlation with drug response

Results	**Prevalence percentage and average**	**Correlations**						
		MMT	**HY**	**UPDRS**	**Duration of disease**	**Age**	**Drug response**	**Dmn side**

Tremor	76,6% 1,77	p:0,86 c:-0,03	p:0,19 c:0,24	p:0,09 c:0,31	p:0,47 c:0,13	p:0,58 c:-0,10	p: 0,17 c:-0,25	p:0,30 c:0,19
Postural reflex	23,3% 1,23	p:0,19 c:-0,24	p:0,35 c:0,17	p:0,48 c:0,13	p:0,53 c:0,12	p:0,39 c:0,16	p: 0,07 c:-0,33	p:0,12 c:0,29
P. walking	63,3% 1,63	p:0,38 c:-0,16	**p:0,00** **c:0,59**	**p:0,00** **c:0,58**	**p:0,00** **c:0,58**	p:0,58 c:0,10	**p:0,02** **c:-0,43**	p:0,13 c:0,28
Bradykinesia	76,6% 1,77	p:0,80 c:-0,04	**p:0,00** **c:0,55**	**p:0,00** **c:0,58**	**p:0,00** **c:0,48**	p:0,15 c:0,26	**p:0,03** **c:-0,40**	p:0,52 c:0,12
Bradyrhythmia	86,6% 1,87	p:0,92 c:-0,01	p:0,18 c:0,25	p:0,15 c:0,26	p:0,88 c:0,02	p:0,59 c:-0,10	p: 0,56 c:-0,11	p:0,40 c:0,15
Asoc. mv. loss	80% 1,80	p:0,26 c:-0,20	p:0,25 c:0,21	p:0,08 c:0,32	p:0,15 c:0,26	p:0,54 c:-0,11	p: 0,28 c:-0,20	p:0,49 c:0,13
Rigidity	56,6% 1,57	p:0,77 c:-0,05	**p:0,02** **c:0,41**	**p:0,01** **c:0,43**	p:0,39 c:0,16	p:0,25 c:-0,21	p: 0,52 c:-0,12	p:0,85 c:0,35
Meyerson	36,6% 1,37	p:0,14 c:0,27	p:0,38 c:-0,16	p:0,63 c:-0,09	p:0,80 c:-0,04	p:0,18 c:-0,25	P:0,98 c:0,00	p:0,39 c:-0,16
Posture change	60% 1,60	p:0,38 c:0,16	p:0,20 c:0,24	p:0,18 c:0,25	p:0,25 c:0,21	p:0,25 c:0,21	p:0,51 c:-0,12	p:0,14 c:0,27

Spearman's rho correlation analysis

Similarly, there was a significant relationship between the duration of disease and the presence of hallucinations (p: 0.013, c: 0.449) and visual hallucinations 0,03, c: (p: 0.393). While there was no correlation between H&Y stage (p: 0.179, c: 0.252) and hallucination, a significant correlation was found between the UPDRS score and hallucination (p: 0.013, c: 0.432). Significant values were not obtained (p>0.05) between the MMT scores and the presence of hallucinations (c: -0.300) and visual hallucinations (c: -0.332), but a weak negative correlation was observed. The frequency of auditory hallucinations was found to be significantly associated only with MMT (p: 0.04, c: -0.377) (Table 9).

Table 9. Hallucination frequency and its correlation with other parameters

	Average a	Correlations				
		HY	UPDRS	Duration of disease	MMT	Age
Hallucinations	1,37 ± 0,490	p: 0,179 c: 0,252	**p: 0,017** c: 0,432	**p: 0,013** c: 0,449	p: 0,113 c: -0,295	**p: 0,038** c: 0,381

V Hallucination	0,77 ± 0,430	p: 0,084 c: 0,320	**p: 0,045** c: 0,370	**p: 0,03** c: 0,393	p: 0,073 c: -0,332	**p: 0,03** c: 0,397
I Hallucination	0,87 ± 0,346	p: 0,727 c: 0,066	p: 0,246 c: 0,218	p: 0,218 c: 0,232	**p: 0,04** c: -0,377	p: 0,813 c: 0,045
T Hallucination	0,90 ± 0,305	p: 1,00 c: 0,00	p: 0,521 c: 0,122	p: 0,377 c: 0,167	p: 0,373 c: 0,169	p: 0,761 c: -0,58

Spearman's rho correlation analysis

4. Discussion

IPD is a neurodegenerative disorder accompanied by motor and non-motor symptoms. Non-motor features can be seen at all stages and may occur before motor findings (Chaudhuri et al., 2005, Chaudhuri et al., 2008). Besides immobility and slowness, non-motor properties are among the most common complaints of IPD patients (Lee et al., 2007). Non-motor symptoms include symptoms such as hyposmia, autonomic dysfunction, gastrointestinal and sensory problems, neuropsychiatric symptoms, and sleep disorders (Sommer et al., 2004, Haehner et al., 2007, Ziemssen & Reichmann, 2007, Chaudhuri & Schapira, 2009). The importance of non-motor symptoms lies not only in their frequent occurrence, but also in their great impact on the patient's quality of life (Lee et al., 2007).

Early motor symptoms in IPD typically begin in one half of the body. Partial involvement is a significant clinical and neuropathological factor in IPD studies. This asymmetrical onset in motor findings continues relatively even in the advanced stages of the disease. Patients with left-side involvement predominantly show right hemisphere pathology, and those with right-sided involvement predominantly show left hemisphere pathology (Kempster et al., 1989). However, this asymmetric involvement was not detected in neuropathological studies in regions other than the extrapyramidal system (Goetz et al., 1989). However, this side involvement in IPD does not seem to be specific to motor symptoms only. For example, it has been observed that the complaints of IPD patients who frequently complain of pain and weakness and who have autonomic symptoms even in the early stages may be more dominant on the affected side (Djaldetti et al., 2001, Djaldetti et al., 2004).

Various studies on lateralization of the brain have revealed conflicting results. In some of these autonomic nervous system functions have been studied in stroke patients. In the Wittling study of 1998, the relationship between the asymmetry of the brain in sympathetic and parasympathetic control of the heart was studied on 45 healthy volunteers. The result is that the left cerebral hemisphere is the more dominant party in the parasympathetic control of cardiac activity, and the right hemisphere of the brain is responsible for sympathetic activity (Wittling et

al., 1998). In a study conducted in Turkey in 1999, RR interval changes (RRIV) and SDR were tested on 32 stroke and 29 healthy controls to evaluate the effects of ischemic and haemorrhagic brain lesions on the sympathetic and parasympathetic system. According to the results, researchers concluded that reflex sympathetic activity is represented in both brain hemispheres, whereas parasympathetic activity is predominantly represented in the right hemisphere of the brain, contrary to the 1998 Wittling study (Erciyas et al., 1999). Distinct unilateral migraine patients are natural clinical examples of inequality between brain hemispheres. In 2004, Avnon et al. examined the trigemino-parasympathetic reflex responses in the inter-attack period on 30 female patients with a diagnosis of unilateral migraine. The results revealed that there are differences in cutaneous and cardiac parasympathetic responses between right and left-sided migraine patients. Left-sided migraineurs showed a higher rate of vasodilation and more bradycardia response in forehead measurements than those with right-sided migraine, and they showed higher somato-parasympathetic sensitivity (Avnon et al., 2004).

The asymmetry of the brain emerges as a universal phenomenon that defines the function of the entire nervous system (Davidson & Hugdahl, 1995). This asymmetric involvement has been demonstrated both clinically and neuropathologically in IPD studies (Kempster et al., 1995). In our study, in light of this information, we aimed to shed some more light on this area by examining the relationship between asymmetry in IPD and autonomic nervous system involvement, which has not been clarified yet. When looked in terms of sociodemographic characteristics, the average age of our patients between the ages of 50-83 was 68.8. 66.6% of the patients were men and 33.3% were women. According to the literature, IPD typically begins in people over the age of 50. The disease incidence rate is higher in men in all IPD studies (Ropper & Brown, 2006, Mehndiratta et al., 2011 4). In this respect, our findings are compatible with the literature.

The duration of the disease was found to be 59.9±47.3 months in a wide range. The mean UPDRS values of the patients were found as 30 points, and the mean MMT values were 26 points. According to H&Y staging, the disease severity of patients with IPD was found to be the most frequent stage 1.5. It was thought that this may be since patients whose general medical condition and mental status were poor and who could not comply with the instructions in detailed examinations and tests were not included in the study when selecting the patients. Also, when the patients were evaluated according to their MMT scores, it was observed that they did not show significant dementia and received an average score above the cut-off value of 24 points, which can be explained by the low disease stages and the average duration of the disease around 5 years.

According to the literature that supports this, dementia in IPD is a common complication and is an integral part of the neurodegenerative process. Severe motor impairment also has a synergistic effect on dementia (Chaudhuri & Tolosa, 2009). In a prospective study, the mean annual decrease in MMT score over four years was found to be 1 point in patients without dementia (Aarsland et al., 2004). Considering this information, according to values such as average 5-year disease duration, H&Y stage 1.5, MMT 26 points appears as an expected result. However, it is necessary to state an important point as a limitation in the study; despite its widespread use as a measure of global cognitive function, relying entirely on a traditional single MMT score such as 24/30 would not be a sensitive approach because this tool does not give healthy measures of executive function and has a strong propensity to memory deficits. Therefore, although patients score above this limit value, they may still suffer from dementia (Chaudhuri & Tolosa, 2009).

IPD started from the right side in 63.3% of the patients and from the left side in 36.6% of the patients. When we look at the literature, we can see the higher number of patients with right side onset as an expected result. Because even in a healthy brain, there is less dopamine in the right-sided striatum, suggesting that the left hemisphere is more sensitive to large losses of dopamine than the right hemisphere (Del Tredici et al., 2010).

In our study, a total of 12 autonomic signs, including sweating, oily skin, hair and hair loss, leg oedema, constipation, dysphagia, orthostatic hypotension, frequent urination, urinary urgency, nocturia, incontinence, and impotence, were questioned, each was scored with a score of 1 and the mean value was found to be 5.2±2.3. When the autonomous total score was compared with the dominant side, no significant results were found in parametric and non-parametric tests. When each autonomic findings were compared separately, there was no significant result.

Various studies have been conducted investigating autonomic findings, lateralization of the brain and disease asymmetry, some evidence supporting a significant relationship has been found, and no significant relationship has been found in others. An important one is a long-term study conducted in 2010 in Spain on a large sample (Cubo et al., 2010). In a national, multicentre, longitudinal study conducted on a sample of polyclinic patients diagnosed with IPD according to BKPDBB criteria, a total of 241 patients were divided into 2 groups as those with mild asymmetry in motor symptoms and those with obvious asymmetric involvement. Following the initial evaluation, the patients were re-evaluated after a 1-year follow-up, and their motor characteristics, non-motor symptoms, and psychosis severity were scored. As a result, it has been shown that IPD with mild to moderate motor asymmetry does not affect non-motor symptoms,

while very pronounced asymmetry only affects psychosis. In other words, it was concluded that the severity of psychosis increased disproportionately in right dominant IPD, and motor asymmetry did not significantly affect the severity of other non-motor symptoms. This suggests that non-motor symptoms reflect a much wider area of brain involvement. The value of the study lies in the fact that it is the first longitudinal study using a highly representative sample and the inclusion and exclusion criteria were made by movement disorder specialists. Besides, the most important non-motor symptoms were determined using scales prepared specifically for the IPD population. According to the hypothesis formed as a result of this study, despite the main pathological elements of IPD such as asymmetric dopaminergic degeneration located in SNPC, the idea that neuron degeneration may be more or less symmetrical in other systems, including mesocortical dopaminergic cells, noradrenergic (locus ceruleus), serotonergic (dorsal rafe nucleus), cholinergic (Meynertin basal nucleus), histaminergic and peptidergic systems, which are responsible for non-motor symptoms (Lang et al., 2004). As a result of our study, no correlation was found between any of the autonomic findings and asymmetric involvement. The sample size of our study was small, and the tests we used were not standardized tests, for example in measuring psychosis or in autonomic symptom screening. The presence of psychosis was investigated using questions in the UPDRS and questions regarding the presence and type of hallucinations. A specific scale such as SCOPA-AUT was not used in questioning autonomous findings. These also constitute the weaknesses of our study.

On the contrary, studies that can establish a relationship of motor asymmetry with at least a specific part of the autonomic findings have also been included in the literature. In another study conducted in 2010, it was aimed to elucidate the phenomenology of pain complaints in IPD, the effect of mood disorders on pain and their relationship with hemispheric asymmetry. It was thought that if negative mood is directed by lateralized brain functions, the affective and cognitive components of pain may also be lateralized. In this pilot study, pain sensitivity was significantly higher in IPD than in the control group. McGill pain scale scores in left-onset IPD were found to be significantly correlated with mood disorders, but the same relationship was not detected in right-affected patients. The relationship between mood and pain has been demonstrated with a striking, almost perfect correlation in IPD patients with left involvement. Also, it has been proven that there is a difference in the expression of pain symptoms among IPD patients as a reflection of the side involvement. In patients with left-sided onset and right hemisphere pathology, the intensity of ongoing pain was reported more than in the control group (Mc. Namara et al., 2010).

In this study, we see that a specific one of the non-motor findings has been studied in detail. In our study, separate scales were not used for each symptom. Symptom questioning was completed based on the patient's history; only orthostatic hypotension measurements were measured by objective tests.

Autonomic system involvement affects a significant portion of people with IPD, approximately 60-80%. The most common signs of autonomic disorder are constipation, orthostatic hypotension, bladder disorders, sweating disorders and impotence, respectively (Korchounov et al., 2005). Bladder disorders were the most common autonomic disorders in our study. This was followed by constipation, impotence, sweating disorder and orthostatic hypotension. The first five most common findings were consistent with the literature.

The belief that non-motor symptoms develop only in advanced stages in IPD is a common but false belief. The data of some prospective studies have shown that some non-motor findings such as decreased sense of smell, constipation, depression, and impotence may appear before motor findings and diagnosis of IPD in IPD (Chaudhuri & Healy, 2006, Tolosa et al., 2007). In some studies, using the non-motor symptom questionnaire (NMSQuest) (Del Tredici et al., 2010), 30 non-motor symptoms in IPD were questioned, and it was found that they can be seen in every stage from the early stages to the advanced stages of IPD and show a strong correlation with the duration of the disease. In our study, the duration of the disease and autonomic findings were compared. When looking at individual autonomic findings in our study, a significant correlation was found only with constipation (p: 0.019), frequent urination (p: 0.03) and urinary urgency (p: 0.019), however, when the total autonomic score was examined, a significant and moderate-good correlation was found between the duration of the disease. In this respect, our results were compatible with the literature. Besides, in our study, when the onset time of autonomic findings was compared with the time of onset of IPD and the patient's age, no correlation was found between age and autonomic involvement duration, while there was a good correlation between the duration of IPD disease and the duration of autonomic involvement (c: 0.67) Thus, the false belief that autonomous findings are seen only in advanced stages was once again refuted by our findings.

When H&Y and autonomic findings were compared, no significant relationship was found between individual or total scores and H&Y stages. In the literature, we see that the opposite results were obtained in some cross-sectional and multicentre studies using large-scale NMSQuest, including autonomous findings. In one of them (Martinez-Martin et al., 2007)

conducted with the participation of 545 patients, it was found that the prevalence of NMS increased significantly with the disease severity determined by H&Y staging. Similar results were obtained from the study conducted by Chadhuri, an international pilot study conducted with 242 IPD patients (Chadhuri et al., 2007). In our study, the mean H&Y stage of the patients was found to be 1.5. The mean duration of disease was 5±3.9. In the aforementioned studies, the mean age of the patients was similar, but the majority of the participants were between H&Y stage 2-3. Mean duration of disease was higher than the patients in our study. It is possible that there was no correlation between stage and autonomic score, since the majority of our patients were in the early stages. However, we were able to find a weak correlation between disease severity measured by UPDRS and autonomic score (p not significant, c: 0,337).

As expected, there was a positive correlation between disease duration and H&Y stages and UPDRS scores. As expected, a negative correlation was found between H&Y and UPDRS scores and MMT scores. As it is known, IPD is a neurodegenerative disease that progresses with age, and dementia that occurs in advanced stages is an integral part of this process because of a long-term pathological progression. In this respect, our results are in full compliance with the literature.

No significant correlation was found between the dominant affected side and the H&Y and UPDRS scores. In a multicenter case-control study in 2013, 136 patients with a diagnosis of IPD for more than 20 years and not exceeding H&Y stage 4 were compared with 134 control iPD cases. It was observed that patients with early onset of the disease, left-handed or left-dominant involvement, continue their mobility, not exceeding stage 4 of the disease stages in long disease periods (Munhoz et al., 2013). Another large sample study was conducted with 307 patients in 2008, and no relationship was found between disease severity measured by UPDRS and bilateral involvement (Yust-Katz et al., 2008). We see that there are not enough studies yet to determine the relationship between bias and disease severity measured by H&Y and UPDRS, and existing studies do not report a single consensus opinion. Disease drug response and the dominant affected side, disease duration, H&Y stage, and UPDRS scores were compared. Disease drug response had no correlation with any of these. In the literature, there are studies showing the relationship between treatment efficacy and prognosis and the dominant affected side. Levodopa, as it is known, has the greatest effect on the dominant affected side. According to the results of some animal studies, it has been shown that there are more dopamine receptors in the right brain and a greater up-regulation of D2 receptors in the right striatum because of ipsilateral lesions (Giardino, 1996, Xu et al., 2005). By adapting these findings to humans, it was argued that IPD-

related symptoms caused by right hemisphere dopaminergic system degeneration have deeper effects than those in the left hemisphere, and that the left basal ganglia compensate for nigral cell loss due to striatal dopamine deficiency. This lateralization of the dopamine receptor population in the basal ganglia may lead to the conclusion that the left-sided-onset IPD has a worse prognosis than the right (Riederer & Sian-Hülsmann, 2012). These results seem to contradict with the previous literature, which argues that the sensitivity of the left hemisphere to dopamine deficiency and the prognosis of PH with right-sided involvement is worse (Haaxma et al., 2010, Cubo et al., 2010). In a study published in 2007, 35 patients with IPD with asymmetric onset, relatively young and without very severe motor symptoms and 12 healthy controls were examined. In this study, in which cognitive functions were examined in more detail with various tests, no relationship was found between the severity of motor symptoms and some specific symptoms and asymmetry and treatment intake (Tomer et al., 2007).

When compared with the clinical findings of IPD, there was a weak correlation between disease drug response and change in posture, while a significant negative correlation was found with bradykinesia. In other words, it was concluded that patients without bradykinesia had better response to treatment as expected. It is known in the literature that rigidity-bradykinesia subgroups show a rapid disease progression (Gasparoli et al., 2002). This subgroup distinction is constantly used to predict the severity of the disease (Shinotoh et al., 2000). Various studies have shown that bradykinesia-predominant patients also have lower cognitive functions (Huber et al., 1992, Loius et al., 1999). In a literature review conducted in 2012, it was stated that tremor dominant IPDs did not show significant cognitive impairment, the severity of the disease was milder, very few patients in this group showed bilateral involvement and showed a more benign disease form with slow motor symptoms (Riederer & Sian-Hülsmann, 2012). Our results are in line with the results of previous studies in the literature in this respect.

When the relationship between disease duration, age, H&Y, UPDRS, MMT and hallucinations was examined, a significant relationship was found between age and visual hallucinations (c: 0,397, p: 0,03). Likewise, there was a significant relationship between the duration of the illness and the presence of hallucinations and visual hallucinations. No correlation was found between H&Y stage and hallucinations, but a significant correlation was found between UPDRS score and hallucination. A weak negative correlation was observed between MMT scores and hallucinations. Hallucination is a very common finding in studies on IPD. The most common of these are visual hallucinations and illusions. According to the literature, 1/3 of the patients have visual

hallucinations and 3/4 of the patients develop visual hallucinations within 20 years during follow-up (Diederich et al., 2009). Hallucination is usually seen in normal consciousness, without delirium and has a chronic course (Fénelon et al., 2000). Risk factors are advanced age, long disease duration, cognitive impairment, severity of IPD symptoms, sleep disturbances and visual disturbances (Fenelon et al., 2010). In our study, hallucination was found to be associated with advanced age, prolonged disease duration, and disease severity measured by UPDRS. A weak negative correlation was found between MMT and hallucinations. Hallucination is known to be a risk factor for cognitive impairment and dementia (Factor et al., 2003). In these respects, all our results seem to be in harmony with the results of past research.

5. Conclusion

Looking at the results, it was determined that IPD was more common in men, right-sided involvement was more common than the left, and as the duration of the disease increased, the severity of motor symptoms increased, and the severity of autonomic involvement increased. Besides, it was concluded that autonomic findings can be seen from the early stages of the disease. It was demonstrated that patients without bradykinesia responded better to treatment. It was observed that the incidence of hallucinations increased as the patients' age and disease severity increased. No relationship was found between the dominant side and the severity of the disease. When the relationship between the dominant side and autonomic involvement, which is the aim of our study, was examined, no significant relationship was found between them.

Acknowledgement

None.

Conflicts of interest

The authors declare that there are no potential conflicts of interest relevant to this article.

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