NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

RESEARCH ARTICLE

Arch Neuropsychiatry 2025;62:77–83
https://doi.org/10.29399/npa.28670

Idiopathic Parkinson's Disease and Neuro-ophthalmological Findings: A Study on Neurodegeneration in the Retinal Nerve Fiber Layer and Cognitive Functions

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ABSTRACT

Introduction: This study was designed to explore the relationship between retinal nerve fiber layer (RNFL) thickness and cognition in Idiopathic Parkinson's disease (IPD) patients without visual symptoms or diagnosis of dementia.

Methods: Groups of patients with idiopathic Parkinson's disease and healthy controls were compared ophthalmologically using optical coherence tomography (OCT) and cognitively through neuropsychological tests.

Results: The findings highlighted a pronounced RNFL thinning, especially in the right nasal inferior quadrant of IPD patients compared to the control group. Almost half (47%) of the subjects in the IPD group exhibited issues in one or multiple subcomponents of Addenbrooke's Cognitive Examination-Revised (ACE-R). At the same time, the study suggested that effects in the visuospatial domain may be associated with disease severity in IPD patients. However, the investigation could not establish a direct association between the severity or duration of the disease and OCT measurements. A correlation was observed between certain ACE-R scores and some RNFL quadrants.

Conclusion: In conclusion, the inception phases of IPD are characterized by discernable visual pathologies and cognitive anomalies. The thinning of the RNFL, which can be identified through OCT, might serve as a pivotal tool for tracking the early progression of IPD and formulating intervention strategies. That being said, more comprehensive studies are essential to wholly understand OCT's role in the early diagnosis and monitoring of IPD.

Keywords: Cognition, Idiopathic Parkinson's disease, optical coherence tomography, retinal nerve fiber layer.

Cite this article as: Çekiç S, Piri Çınar B, Acıman Demirel E, Akdemir MO, Çelebi U, Açıkgöz M et al. Idiopathic Parkinson's Disease and Neuro-ophthalmic Findings: A Study on Neuro-degeneration in the Retinal Nerve Fiber Layer and Cognition. Arch Neuropsychiatry 2025;62:77–83.

INTRODUCTION

Idiopathic Parkinson's Disease (IPD) is a progressive neurodegenerative disorder of the central nervous system with an insidious onset (1). A study in the United States reported a mean prevalence of IPD of 1.6% among people aged 65 years and older (2). It is more commonly observed in males compared to females (1). Idiopathic Parkinson's disease predominantly begins between the ages of 50 and 60, with age being a significant risk factor (1). Factors such as toxic agents, rural and industrialized living, and genetics are believed to play roles in its etiology; however, multifactorial causes are often considered responsible (1,3). The neuropathology defines the loss of dopaminergic neurons in the substantia nigra pars compacta and the abnormal accumulation of synuclein-containing Lewy bodies and cytoplasmic inclusions (1,3). The typical clinical manifestations of the disease emerge due to this neuronal loss. Primary diagnostic criteria for IPD include tremor, rigidity, bradykinesia-hypokinesia, bradymimia, postural instability, walking disturbances, flexion posture, and the freezing phenomenon (1).

Highlights

- **Cognitive and retinal changes can be observed in the early stages of IPD.**
- **RNFL measurement may be useful to determine early intervention strategies.**
- **OCT may be a tool to examine risk factors for early cognitive impairment.**

Idiopathic Parkinson's disease is a heterogeneous clinical condition impacting both motor and non-motor functions. Among the non-motor symptoms are depression, cognitive impairments, sleep disorders, constipation, hyposmia/anosmia, and visual disturbances (1,4).

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Received: 02.12.2023, **Accepted:** 08.05.2024, **Available Online Date:** 20.02.2025

Cognitive impairment is one of the non-motor symptoms of IPD, significantly affecting the quality of life. Cognitive function impairments in IPD can range from mild cognitive impairment to IPD dementia and often involve disturbances in visuospatial functions, memory, attention and alertness, planning, and language (5). Recent studies concerning visual system disturbances, one of the non-motor symptoms of IPD, indicate the retina's involvement in IPD (4,6). In IPD, due to dopamine loss, it is believed that there is a reduction in dopaminergic amacrine cells, indirectly leading to a decrease in retinal ganglion cells. This, in part, may result in the thinning of the retinal pigment epithelium (7,8). Visual findings in IPD can manifest as a decline in contrast sensitivity, impaired color vision, prolongation in visually evoked potentials, and changes in amplitude and latency in electroretinograms (7). Optical coherence tomography (OCT) is a non-invasive, rapid, objective, and repeatable technique to obtain cross-sectional images of the retina and optic disc (7,8). It has recently become a widely used method for detecting structural axonal damage in optic nerve diseases. The thickness of the peripapillary retinal nerve fiber layer (RNFL) is measured and interpreted to provide insights about axonal loss. Although there are studies investigating the relationship between disease severity, quality of life, cognition, and OCT parameters in IPD, data on the relationship between cognition and OCT parameters in IPD patients without dementia are limited (7–14). This study aimed to examine neurodegeneration in IPD based on RNFL thickness and cognition, which are indicators of neurodegeneration, and to review the relationship between cognition and RNFL thickness in IPD patients without visual symptoms or diagnosis of dementia.

METHODS

Study Design

Participants: The study included 34 patients diagnosed with IPD under the care of Bülent Ecevit University Faculty of Medicine Neurology Clinic. Twenty-one healthy volunteers with similar demographic characteristics and without any chronic neurological or ocular diseases were selected as the control group. All participants provided informed consent by signing an informed consent form.

Inclusion criteria for IPD group: Patients must have been diagnosed with IPD received at least five years prior, be in stages 1, 2, 3, or 4 according to the Hoehn and Yahr (HY) Scale, possess sufficient hand functionality to execute the tests, not having dementia as determined by Mini-Mental State Examination (MMSE) (>24), have no any additional neurological disease that might affect cognitive status or have no any ophthalmological symptoms or diseases that might affect the RNFL.

Exclusion criteria for both groups: It includes the presence of neuropsychiatric diseases that might influence cognitive status, diabetes with retinal pathology, glaucoma, intraocular pressure exceeding 21 mmHg, congenital color vision defects, congenital optic disc anomalies, ocular diseases leading to opacities, visual acuity less than 0.6, advanced refractive errors, and illiteracy.

Data Collection

Demographic information of both the patients and the volunteers was recorded. Clinical assessments and disease severity of the IPD group were determined using the Unified Parkinson's Disease Rating Scale (UPDRS) and HY staging. Participants' neuropsychological statuses were evaluated using MMSE, Addenbrooke's Cognitive Examination-Revised (ACE-R), and Digit Span Test, while their depression statuses were assessed using Geriatric Depression Scale-15.

Retinal Nerve Fiber Layer Thickness Measurement: The RNFL thicknesses were measured using the OCT device (Spectralis®; Heidelberg Engineering, USA) by the same expert at the Ophthalmology Clinic.

Clinical Evaluation

The UPDRS is a common scale consisting of 50 items. The first section encompasses 13 items related to non-motor issues, the second section contains 13 items concerning motor problems, the third section has 18 items related to motor examination, and the fourth section includes six items about motor complications (15). The HY scale is a staging method that can simply measure the progression and disability level of IPD (15).

Neuropsychological Assessment

In our study, both the IPD group and healthy volunteers underwent neuropsychological assessment using the MMSE, ACE-R, and Digit Span Test (both forward and backward). Mini-Mental State Examination is a simple cognition assessment scale with a threshold value of 23/24, evaluated out of 30 points for the diagnosis of mild dementia (16). ACE-R, which is short, inexpensive, and sensitive in detecting the early stages of dementia and helps distinguish dementia subtypes, is used as a cognitive screening test (17). The Digit Span Test is a Wechsler Adult Intelligence Scale Battery subtest, which evaluates short-term memory and attention (18). The Geriatric Depression Scale-15 was applied to all participants to assess depression.

Measurement of Retinal Nerve Fiber Layer Thickness with Optical Coherence Tomography

The RNFL thickness was assessed using the OCT method (Spectralis®; Heidelberg Engineering). Prior to the procedure, a detailed eye examination, encompassing intraocular pressure measurement and examinations of the anterior segment and retina, was conducted. Retinal nerve fibers were individually evaluated for each eye, and the seven sectors of each eye, global, nasal superior (NS), nasal inferior (NI), nasal, temporal superior (TS), temporal inferior (TI), and temporal quadrants, were assessed. The RNFL was gauged by measuring a circle with a diameter of 3.45 mm automatically placed at the center of the optic disc, and a 6 mm macular area was scanned to measure the thickness of the retina's seven sectors. Macular measurement was performed to exclude other pathologies.

This study has been approved by the Bülent Ecevit University Clinical Research Ethics Committee (14/02/2019, 2019-33-14/02).

Statistical Analysis

Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS) program version 19.0. The power of the study was calculated with G Power 3.1.9.7 after determining the effect size and was found to be 80%. Descriptive statistics of continuous variables in the study include mean, standard deviation, median, and minimum and maximum values. Descriptive statistics of categorical variables include frequency and percentage. Whether the data were suitable for normal distribution was evaluated using Kolmogorov-Smirnov and Shapiro-Wilks normality tests. An independent sample T-test was used to compare normally distributed variables in the two groups, and a Mann-Whitney U test was used to compare variables not normally distributed in the two groups. A Chi-square test was used for categorical variables. Wilcoxon test was used to measure the difference between two related measurements in both eyes. The relationship between continuous variables was analyzed using Spearman correlation analysis. In all statistical analyses, a p-value below 0.05 was considered statistically significant. The relationship between IPD severity, cognition, RNFL thickness, and other independent variables was studied using multiple linear regression analysis and enter and stepwise models.

RESULTS

Thirty-four patients (female/male: 12/22) diagnosed with IPD and 21 controls (female/male: 9/12) were included in the study. The mean age of the IPD group was 64.76±11.29 years, and the mean age of the control group was 66.24±9.73 years. There was no significant difference between gender and mean age (p=0.575 and p=0.623, respectively) (Table 1).

The mean disease duration of the patients was 7.24±4.65 (5–25) years. The average UPDRS score of the patients was 41.15±27.45. The scores of the motor and non-motor sections of the UPDRS scale were evaluated separately. The average motor score of UPDRS was 32.79±20.05 (11–106). The average non-motor score of UPDRS was 6.85±5.7 (1–25). The average HY stage was 1.42±0.64. The distribution of UPDRS score and HY stage by gender was examined. For males, the mean UPDRS score was 30.1±25.9, and the HY stage was 1.3±0.5. For females, the mean UPDRS score was 35±24.1, and the HY stage was 1.6±0.8. There was no significant difference between either genders in terms of UPDRS and HY staging (p=0.538, p=0.378, respectively). When the patients were evaluated in terms of disease onset, 17 patients had left-side onset (50%), 15 patients had right-side onset (44.1%), and two patients had bilateral onset (5.9%). Regarding symptom dominance, 17 patients were rigid-weighted (50%), and 17 patients were tremor-weighted (50%). In addition, 32 patients had right-hand dominance (94.2%).

There was no significant difference between the mean depression score of the patients and the controls (4.41±3.04 and 4.71±4.18, respectively; p=0.910). The average MMSE score of the controls and patients was 28.48±1.91 and 26.91±3.27, respectively; no significant difference was found between the groups (p=0.075). The total ACE-R score was significantly lower in the patients compared to the controls (73.74±12.93 and 82.76±9.39, respectively; p=0.007). When ACE-R subgroups were evaluated separately, the scores for memory, fluency, and language functions were significantly lower in the patients compared to the controls (p=0.021, p=0.029 and p=0.034, respectively). The controls had significantly better scores than the patients in forward counting and a higher total score on the digit span test (p=0.005 and p=0.007, respectively). In terms of gender, no significant difference was observed in either ACE-R total scores and subgroups in the controls. A significant difference was found in language functions between the genders in the patient group. The language functions of male patients were better preserved than those of female patients (p=0.003). All cognitive data of both groups are given in Table 2.

When the OCT parameters of the study group were examined, the mean RNFL value of the right NI quadrant was statistically significantly lower in the patient group than for the healthy controls (p=0.026). There was no difference in terms of gender in the controls (p>0, 05). Meanwhile, the right NS and left TS RNFL were thinner in male patients (p=0.013 and p=0.003, respectively). The patients' characteristics of disease symptom dominance (tremor or rigidity) and lateralized onset characteristics (onset on the right or left side) were also evaluated. There was no difference in cognitive tests and OCT measurements between the tremor-predominant and rigidity-predominant groups (p>0.05). There was no significant difference in cognitive tests and OCT parameters between the groups with right-side and left-side onset symptoms (p>0.05). The relationship between disease onset characteristics and interocular RNFL difference was investigated. The interocular difference tended to be greater in patients with right-side onset. However, the difference was not statistically significant (mean 4±5.35 for left-side onset and 10±19.80 for right-side onset) (p>0.05). All OCT data of healthy and patient groups are given in Table 3.

As a result of correlation analysis, a negative correlation was found between age and ACE-R total score and memory score (rho: -0.396 and -0.410, respectively, p=0.020, p=0.0016). A positive correlation was found between disease duration and disease stage, disease duration and motor symptom scores, and disease duration and non-motor symptom scores (rho: 0.478, 0.448, and 0.418, respectively, p=0.003, p=0.0019, p=0.026). In addition, UPDRS scores were moderately negatively correlated with visuospatial functions (rho: -0.413, p=0.015).

Table 1. Demographic data of study group

	Patient group (N=34)		Control group (N=21)	p value
Mean age ± SD (min-max)	64.76±11.29 (35–91)		66.24±9.73 (48–86)	0.623
Gender (Female/Male)	12/22		9/12	0.575
Duration of education [n (%)]	5 years	70.6%	71.4%	0.726
	8 years	8.8%	14.3%	
	11 years and above	20.5%	14.3%	

SD: Standard deviation.

Table 2. Cognitive test scores of study groups

	Patient group mean ± SD	Control group mean ± SD	p value
MMSE	26.91±3.27	28.48±1.91	0.075
ACE-R	73.74±12.93	82.76±9.39	0.007
Attention and orientation	16.85±2.04	17.57±1.12	0.320
Memory	14.97±5.90	18.43±3.77	0.021
Fluency	8.12±2.30	9.67±2.55	0.029
Language	21.56±3.67	23.29±3.77	0.034
Visuospatial functions	12.53±2.64	13.81±1.94	0.089
Digit span test (forward score)	4.88±1.88	6.29±1.64	0.005
Digit span test (backward score)	3.32±1.68	4.19±1.66	0.054
Digit span test (total score)	8.21±2.97	10.48±2.87	0.007

ACE-R: Addenbrooke's Cognitive Examination-Revised; MMSE: Mini-Mental Status Exam; SD: Standard deviation.

Table 3. Evaluation of RNFL thickness of study groups

	Patient group mean ± SD	Control group mean ± SD	p value
Right RNFL (µm)	95.88±14.97	99.95±12.6	0.665
Right temporal superior RNFL (µm)	130.82±29.89	138±23.17	0.451
Right nasal superior RNFL (µm)	104.03±26.39	117.57±26.74	0.177
Right temporal RNFL (µm)	71.18±14.12	68.62±12.15	0.670
Right nasal RNFL (µm)	72.76±12.97	77.71±12.95	0.193
Right nasal inferior RNFL (µm)	103.68±26.77	121.19±26.54	0.026
Right temporal inferior (µm)	141±28.12	129.43±25.68	0.019
Left RNFL (µm)	98.53±10.87	96.57±14.09	0.216
Left temporal superior RNFL (µm)	129.03±23.62	126.95±28.46	0.472
Left nasal superior RNFL (µm)	116.97±25.89	118.52±32.66	0.863
Left temporal RNFL (µm)	72.38±16.76	71.05±16.47	0.841
Left nasal RNFL (µm)	73.78±18.15	68.33±12.93	0.326
Left temporal inferior RNFL (µm)	136.08±25.95	136.71±25.09	0.611
Left nasal inferior RNFL (µm)	114.50±32.18	115.76±27.47	0.928
N/T index (left) (µm)	1.09±0.45	1.01±0.28	0.623
N/T index (right) (µm)	1.06±0.9	1.16±0.29	0.125

µm: Micrometer; N/T: Nasal/Temporal; OCT: Optical Coherence Tomography; RNFL: Retinal Nerve Fiber Layer; SD: Standard deviation.

Table 4. Results of correlation analysis between OCT parameters and age and cognitive test scores

	Patient group rho (p)
Age & right nasal superior RNFL	-0.363 (0.035)
Age & left temporal inferior RNFL	-0.479 (0.006)
ACE-R score & right nasal RNFL	0.476 (0.04)
Fluency & right nasal RNFL	0.379 (0.027)
Language & right total RNFL	0.535 (0.015)
Language & right temporal inferior RNFL	0.360 (0.037)
Memory & right nasal RNFL	0.419 (0.014)
Memory & right nasal inferior RNFL	0.359 (0.037)
Digit span test-forward score & right nasal RNFL	0.448 (0.008)
Digit span test-forward score& right N/T index	0.447 (0.035)
Digit span test-total score & right nasal RNFL	0.428 (0.011)

ACE-R: Addenbrooke's Cognitive Examination - Revised; N/T: Nasal/Temporal; OCT: Optical Coherence Tomography; RNFL: Retinal Nerve Fiber Layer.

In our study, cognitive dysfunction was observed in 47% of the IPD group according to the normative values of ACE-R matched for age, gender, and education level. However, no statistically significant difference was observed between the normal and cognitively affected groups regarding all OCT parameters. A positive correlation was found between the ACE-R score and right nasal RNFL thickness in the patient group (rho: 0.476). When the relationship between cognitive tests and RNFL was evaluated in detail for verbal fluency in the patients, there was a positive correlation with right nasal RNFL thickness (rho: 0.379). In the patient group, language functions were moderately positively correlated with right TI RNFL thickness (rho: 0.360). Memory functions and right nasal and right NI RNFL thickness were positively correlated (rho: 0.419 and 0.359, respectively) (Table 4).

The relationship between cognitive tests and other independent variables was evaluated using multiple regression analysis and both enter and stepwise methods. While age and duration of education (the duration of education is at least 11 years) were found to be effective on ACE-R scores, other explanatory variables were not found to be statistically significant (Tables 5 and 6).

DISCUSSION

In our study, we aimed to emphasize that neurodegenerative changes may begin in the early period, even in patients without dementia or ophthalmological symptoms. This study has revealed the presence of both visual pathological changes and cognitive impairments in the early stages of IPD. This situation draws attention to the importance of close and multisystemic evaluation of patients, even in early and asymptomatic periods. Although the relationship between RNFL parameters and certain cognitive areas is weak, this finding underscores the importance of evaluating patients from all perspectives. Cognitive dysfunction appeared to be more pronounced in some IPD patients, according to the ACE-R test.

Visual findings in IPD encompass impaired visual acuity, color vision, contrast sensitivity, and motion perception (4). In addition, structural changes and affected electrical activity in the retina without visual loss have been reported in IPD (19). The dysfunction in the dopaminergic system in IPD is not limited to the basal ganglia and could affect the retina

Table 5. Regression analysis results for ACE-R (Enter method) R^2=0.426; F=3.476; p <0.001; Durbin Watson=2.866

	B (95% CI)	SH	Beta	t	p	Simple	Partial	VIF
(Constant)	134.442 (73.442–195.442)	29.332		4.583	0.000			
Gender	-3.622 (-13.131–5.887)	4.572	-0.141	-0.792	0.437	-0.187	0.498	2.008
Age (years)	-0.613 (-1.114- -0.111)	0.241	-0.563	-2.538	0.019	-0.342	0.350	2.858
Duration of illness (years)	0.331 (-0.595–1.257)	0.445	0.125	0.744	0.465	0.102	0.626	1.597
Depression scale	-0.858 (-2.372–0.656)	0.728	-0.216	-1.178	0.252	-0.294	0.272	3.676
Right OCT-total	0.241 (-0.031–0.513)	0.131	0.301	1.845	0.079	0.335	0.574	1.743
Left OCT-total	-0.388 (-0.783–0.007)	0.190	-0.343	-2.045	0.054	-0.088	0.260	3.845
HY scale	-4.076 (-14.298–6.146)	4.915	-0.216	-0.829	0.416	0.029	0.363	2.756
Duration of education								
8 years	6.82 (-7.376–21.016)	6.826	0.164	0.999	0.329	0.069	0.488	2.050
11 years	9.81 (-1.487–21.106)	5.432	0.315	1.806	0.085	0.529	0.589	1.699

HY: Hoehn & Yahr; OCT: Optical Coherence Tomography.

Table 6. Regression analysis results for ACE-R (Stepwise method) R^2=0.255; F=11.247; p=0.002; Durbin Watson=1.681

	B (95% CI)	SH	Beta	t	p	Simple	Partial	VIF
(Constant)	70.60 (66.149–74.971)	2.157		32.717	<0.001			
Duration of education								
11 years	16.440 (6.414–26.466)	4.902	0.529	3.354	0.002	0.529	0.529	1.000

ACE-R: Addenbrooke's Cognitive Examination-Revised.

(19). Patients with IPD have been reported to demonstrate low dopamine levels in the eye structure, and findings of dopaminergic neuronal loss in the entorhinal cortex, lateral geniculate nucleus, and visual cortex support this (8,20,21). It has been reported that dopaminergic amacrine cells and retinal ganglion cells decrease in IPD patients, and there is thinning of the retinal pigment epithelium due to the weakening of synaptic connections caused by these changes (4,7,8). Retinal nerve fiber layer thinning has been noted in neurodegenerative diseases as a parameter indicating axonal degeneration. (7,22,23). In the light of these studies and opinions, it is interesting to examine the changes in RNFL thickness in IPD and the relationships of this change with the clinical parameters of the disease.

The data regarding the affected RNFL in patients with IPD are conflicting. There are studies in the literature reporting that RNFL thickness in IPD patients is similar to the control group (10,24–26). However, there are many interesting studies that found the RNFL to be thinner in IPD patients (8,14,19,27,28). When these studies are examined in detail, Inzelberg et al. found significant thinning in the inferior and temporal quadrants of the RNFL (27). Altintas et al. identified significant thinning in mean RNFL average thickness and thinning in many quadrants of RNFL in the patients (8). Moschos et al. found significant RNFL thinning in the inferior and temporal quadrants in IPD patients without visual loss (19). Another study identified significant thinning in the average RNFL thickness and the superior, inferior and temporal regions (28). Our study found significant thinning in the right NI RNFL quadrant of the IPD group compared to the control group. These contradictory findings in the literature are thought to be due to sample differences and sample sizes. The subject needs to be supported by more comprehensive studies with larger samples. It has been reported in the literature that RNFL thickness is greater in patients using levodopa (29). However, in our study, the treatment options received by the patients were too numerous to allow subgroup analysis. We were unable to comment on this matter. Since RNFL can be affected by multiple factors, results may vary between studies. The issue may need to be examined with a larger sample, comprehensive and longitudinal studies, and meta-analyses. The significant NI RNFL quadrant thinning observed in the patient group in our study suggested that OCT may be a valuable method for monitoring neurodegenerative changes.

The relationship between IPD disease severity and RNFL is unclear. It is thought that OCT measurements may be related to disease severity in parallel with dopaminergic cell loss in the RPE and axonal degeneration in IPD (7,8). Garcia Martin et al. found a negative correlation between RNFL thickness and HY stage in their study. Additionally, in the same study, a relationship was found between foveal thickness and disease severity, which is consistent with the study of Altıntaş et al. Some authors have not found a clear relationship between RNFL thickness and disease severity (12,28,30). We have found no significant relationship between OCT measurements and disease severity or duration. This may be due to the small sample size and the early stage of the patient group.

Considering a study reporting that the nasal and inferior quadrant RNFL is thinner in rigid-dominant patients, our study group was evaluated based on disease onset characteristics (31). No significant relationship was found between clinical features such as symptom dominance and side of symptom onset and cognitive status or OCT findings. Cubo et al. found inter-ocular differences in some OCT parameters in IPD patients with right-sided symptom onset (30). Although there was no significant inter-ocular difference in RNFL measurements of IPD patients in our study, there was a trend for a greater difference in right-sided-onset patients. Furthermore, the right nasal fibers were thinner in patients. These findings may suggest that pathological degeneration can be more pronounced in the dominant (left) hemisphere.

In our study, the total ACE-R score was significantly lower in patients compared to the control group. In this study, cognitive impairment observed with impairment in one or more subcomponents of ACE-R was detected in 47% of the IPD group. In the literature, the prevalence of mild cognitive impairment in IPD is reported as 40% (32). In IPD, impairments related to executive functions, attention, visuospatial domain, and memory can frequently be observed (33). In our study, the subgroups of ACE-R scores regarding memory, fluency, and language functions in patients were significantly lower than in controls. In a study comparing IPD patients with Alzheimer's patients and controls, it was reported that in parallel with fronto-subcortical pathology, patients with IPD had more prominent impairments in fluency, memory, attention, and

orientation. However, they were unable to detect any difficulties in visuo-construction tasks, similar to the findings of our study (34). Our study's findings related to cognitive areas, despite some variability, generally appear to be consistent with the literature.

Some screening tests can detect cognitive impairments in the early stages of IPD (35,36). However, more information is needed about the sensitivity and specificity of these tests. ACE-R, the screening test used in our study, was sufficient to detect previously undetectable cognitive disorders. Considering together with the study using ACE-R to detect cognitive impairments in the early stages of IPD, it seems more logical to follow patients with at least multi-component ACE-R instead of MMSE (35). Additionally, compared to studies examining the relationship between OCT and cognition, evaluation with the ACE-R battery added originality to our study (9,12,14,24).

Our study found no correlation between the UPDRS score and the ACE-R total score. However, a significant correlation was found between the UPDRS score and the visuospatial subcomponent score of ACE-R. Our finding suggests that visuospatial domain involvement, one of the primarily affected cognitive areas in IPD, may also be related to the severity of the disease, but more detailed studies should support it.

The data on the relationship between OCT findings and cognitive status in non-demented IPD patients is limited. In our study, the patient group had a significantly thinner right NI RNFL value and lower ACE-R score. We did not detect any significant difference in OCT findings between those with low ACE-R scores and those with normal scores in the patient group. However, in correlation analysis, we detected a relationship between ACE-R score and right nasal RNFL thickness and between some subgroups of ACE-R and some RNFL quadrants. Although weak, this data made us think that OCT is a method worth investigating in predicting early cognitive impairment. When we look at the literature, Pillai et al. did not find a correlation between the severity of cognitive impairment and RNFL (24). However, this study did not include only IPD patients (24). As a result of their study in non-demented IPD patients, Leyland et al. reported that the thinner ganglion cell layer and inner plexiform layer were associated with a higher risk for the development of dementia (9). In their study on IPD patients, Sung et al. reported that macular ganglion cell-inner plexiform layer thickness parameters showed a stronger relationship with cognitive functions (12). However, measuring this layer with the device used in our study was impossible. Utilizing advanced OCT methods to make these measurements in future studies may provide more detailed information. As a result of their logistic regression analysis, Chang et al. found that thinner RNFL was associated with cognitive impairment (14). Recent longitudinal studies with more robust designs have stated that the risk of cognitive decline during follow-up is higher in subjects with thinner RNFL values at baseline (13,37). Although we could not obtain robust data in our study due to its cross-sectional nature and small sample size, when considered together with the current data in the literature, OCT seems to be a method open to development that may be useful to evaluate in early-stage IPD patients and will contribute to our prediction of cognitive decline. More comprehensive studies should be conducted to evaluate whether OCT can be used as a tool to evaluate the risk factors of cognitive impairment in early-stage patients.

In our study, a difference was observed between genders in the IPD group in terms of both cognitive tests and OCT findings. The right NS and left TS RNFL were thinner in men compared to women. There is limited data in the literature about the gender difference in RNFL thickness in IPD. While macular measurements are reported to be thicker in men in OCT measurements in the literature, no significant difference was reported in RNFL (38) However, this study is not related to IPD. The relationship between male gender and RNFL in our study is an exciting aspect to explore. It is important to note that a more comprehensive analysis with a larger patient sample is necessary to shed further light on this relationship.

Our study revealed that male patients tended to have better-preserved language functions when compared to female patients. However, it is important to highlight that even though both male and female patients exhibited comparable levels of brain hypometabolism, women with mild cognitive impairment demonstrated a notable advantage in terms of verbal memory (39). Furthermore, in another study involving individuals with IPD, it was observed that women displayed better verbal functions (40). The advantage women demonstrate over men in terms of verbal memory might signify a form of cognitive reserve, potentially delaying the decline in verbal memory until more advanced stages of pathology. The finding that language functions were better in men in our study contradicts existing literature. This discrepancy may be attributed to our study's relatively small number of patients, and it should be considered when evaluating our results.

The strengths of our study include the use of comprehensive testing and evaluation methods to compare early-stage IPD patients with a healthy control group and the attempt to provide an in-depth look at the different cognitive and visual aspects of IPD in its initial stages. The cross-sectional nature of our study presents a limitation, as it needs to provide insight into how results might change over time. Another area for improvement in our study is that we could not precisely determine when changes in RNFL began.

Current findings indicate the presence of cognitive impairments and visual pathological changes in the early stages of IPD. This could be crucial in monitoring the progression of the disease and determining intervention strategies during its early stages. The routine use of OCT as an assessment tool in patients suspected of IPD might be beneficial for determining the presence and severity of visual pathology at early stages. Developing OCT application protocols and artificial intelligence algorithms for IPD patients may provide earlier and more accurate detection of retinal changes. Since OCT is a sensitive imaging method that can detect thinning in the RNFL, it can be used routinely in the follow-up of IPD patients and documentation of neurodegeneration. By using OCT in a broader patient group, it may be possible to determine whether thinning in specific RNFL regions predicts the progression of the disease. Although the weak relationship between cognitive tests and OCT findings does not fully prove our hypothesis, OCT measurement is a notable method to provide close monitoring in early-stage patients and evaluate risk factors for cognitive impairment. The combination of OCT measurements and cognitive tests may be helpful as a quantitative, easy, and noninvasive measurement method to understand and monitor the neurodegenerative process in patients multisystemically.

In conclusion, more in-depth and comprehensive studies are needed to fully understand the potential of OCT for the early diagnosis of cognitive impairment in IPD. This could play a critical role in determining early intervention strategies and enhancing the quality of life for patients.

Ethics Committee Approval: This study has been approved by the Bülent Ecevit University Clinical Research Ethics Committee (14/02/2019, 2019-33-14/02). All procedures performed in studies involving human participants were in line with the ethical standards of the institutional and national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The data was obtained from our hospital records prospectively for the study.

Informed Consent: Informed consent was obtained from all participants for the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- SÇ, BPÇ; Design- SÇ, BPÇ, MOA; Supervision- SÇ, BPÇ, MOA, EAD, UÇ, MA, HTA; Resource- SÇ, BPÇ, EAD; Materials- SÇ, BPÇ, EAD, MOA; Data Collection and/or Processing- SÇ, BPÇ, MOA; Analysis and/or Interpretation- SÇ, HTA, EAD, BPÇ, MOA, UÇ, MA; Literature Search- SÇ, BPÇ; Writing- SÇ, BPÇ; Critical Reviews- SÇ, BPÇ, EAD, MOA, UÇ, MA, HTA.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: There was no funding for this study.

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