Retinal Morphological Changes during the Two Years of Follow-Up in Parkinson's Disease

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Research article

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Abstract

Background: The study aims to investigate the relationship between the progression of idiopathic Parkinson's disease (IPD) and retinal morphology.

Methods: The study was carried out with 23 patients diagnosed with early-stage IPD (phases 1 and 2 of the Hoehn and Yahr scale) and 30 age-matched healthy controls. All patients were followed up at least two years, with 6-month intervals (initial, 6th month, 12th month, 18th month, and 24th month), and detailed neurological and ophthalmic examinations were performed at each follow-up. Unified Parkinson's Disease Rating Scale part III (UPDRS Part III) scores, Hoehn and Yahr (H&Y) scores, best-corrected visual acuity (BCVA), intraocular pressure (IOP) measurement, central macular thickness (CMT) and retinal nerve fiber layer (RNFL) thickness were analyzed at each visit.

Results: The average age of the IPD and control groups was 43.96 ± 4.88 years, 44.53 ± 0.83 years, respectively. The mean duration of the disease in the IPD group was 7.48 ± 5.10 months at the start of the study (range 0-16). There was no statistically significant difference in BCVA and IOP values between the two groups during the two-year follow-up period ($p > 0.05$, $p > 0.05$, respectively). Average and superior quadrant RNFL thicknesses were statistically different between the two groups at 24 months and there was no significant difference between other visits ($p = 0.025$, $p=0.034$, $p > 0.05$, respectively). There was no statistically significant difference in CMT between the two groups during the follow-up period ($p > 0.05$).

Conclusion: Average and superior quadrant RNFL thicknesses were significantly thinning with the progression of IPD.

Background

Idiopathic Parkinson's disease (IPD) is the second most common neurodegenerative disease following Alzheimer's disease. The prevalence of IPD, which is a chronic and progressive disease, is 1% in the world in individuals aged 60 and over. Non- motor symptoms are very frequent in all stages of Parkinson’s disease (rigidity, bradykinesia, tremor) [1, 2].

In addition to motor symptoms, non-motor symptoms such as depression, dementia, autonomic symptoms, REM sleep behavior disorder, and visual complaints and visual hallucinations can also be seen in IPD. Parkinson’s disease is now recognized as a multisystem, multi-neurotransmitter (dopaminergic, cholinergic, serotoninergic, noradrenergic) dysfunction-related heterogeneous disorder, which we know since the Braak staging[3]. Amacrine and interplexiform cells in the retina are rich in dopamine neurotransmitter [4]. It has been reported that visual pathologies in IPD patients may be due to dopamine reduction in amacrine cells in the retina[5, 6]. Moreover, in post-mortem studies, dopamine levels in the retina were found to be decreased in IPD patients [7].

Retinal structures, which are an extension of the central nervous system, are of interest in terms of the investigation of the pathology of neurodegenerative diseases. Optical Coherence Tomography (OCT) is a fast, objective, non-invasive and sequential measurement method used to evaluate retinal morphology. With the Spectralis OCT device, all retinal layers such as retinal nerve fiber thickness (RNFL), central macular thickness (CMT) and retinal pigment epithelium can be seen and their thickness can be measured separately. Studies have shown that OCT can be a potential biomarker candidate since it shows changes in RNFL thickness in IPD [8]. According to the literature, it has been reported in many studies that RNFL thickness is reduced in IPD. However, in some other studies, there was no significant difference between the IPD and control groups in terms of RNFL thickness [9]. There appears to be a contradiction between the results.

Also, there are very few studies in the literature evaluating the relationship of RNFL values measured by the OCT in IPD patients with the progression of the disease.[10, 11]

In this study, we aimed to evaluate the correlation between IPD progression and changes in RNFL thicknesses and CMT values and whether progressive neurodegeneration continues by examining changes in the RNFL and CMT during two-year (with six-month intervals) follow-up of patients diagnosed with IPD.

Methods

The study was carried out with 23 patients diagnosed with early-stage IPD (disease duration 0–16 months) and 30 healthy controls. Phases 1 and 2 of the Hoehn and Yahr scale were defined as early-stage IPD. [12] The study was conducted between January 2015 and December 2017 in the neurology and ophthalmology clinics of Sakarya University Training and Research Hospital. Patients' informed consent and the approval of the local ethics committee were obtained for the research. Trial Registration Number:71522473/050.01.04/97

All patients were followed up for at least two years, with 6-month intervals (month 0, month 6, month 12, month 18, and month 24), and detailed neuro-ophthalmic examinations were performed by the same clinicians at each visit. Unified Parkinson's Disease Rating Scale part III (UPDRS Part III) scores and Hoehn and Yahr (H&Y) scores were measured to evaluate the severity of the disease in all rounds of the IPD patients. Diabetes mellitus, hypertension, high refraction defects (> 5 diopters of spherical equivalent or > 3 diopters of astigmatism), glaucoma, retinal detachment, or degeneration, uveitis, ocular surface disease, optic neuropathy, and patients with a history of intraocular surgery and trauma, and patients with a pathology (dense cataract, corneal opacity, etc.) that prevents high-quality retinal image (signal strength ≥ 6) were excluded from the study.

Ophthalmic evaluation

Detailed ocular examinations including best-corrected visual acuity (BCVA) in the Snellen scale, intraocular pressure measurement using Goldmann applanation tonometry, slit-lamp biomicroscopic

examination, and dilated funduscopic examination using a 90-diopter lens was performed and recorded at each visit. Spectral-domain OCT (Cirrus HD OCT, Carl Zeiss Meditec, Dublin, CA, USA) device was used for RNFL and CMT measurements in all the patients. This device performs RNFL measurements using the "Optic Disc Cube 200 × 200" method. In this method, the OCT device places the scan ring of 3.46 mm diameter at the optic disc center and measures the average thickness of four quadrants (superiorly, inferior, nasal and temporal), each of which is 90° from the peripapillary region. Average and four-quadrant RNFL thicknesses were measured and recorded at each visit. In addition, the CMT (the mean central subfield thickness) measurements of all patients were performed. The mean central subfield thickness is defined as the mean retinal thickness within a 1-mm circle centered on the fovea.[13] CMT was evaluated by using a macular thickness scanning protocol with the Cirrus HD OCT device after pupil dilatation. Standard macular imaging consisted of the macular cube (512 × 128) and the 5 Line Raster scanning protocols (Carl Zeiss, Carl Zeiss Meditec, Dublin, CA) [14].

Statistical Analysis

SPSS 24.0 (IBM SPSS Statistics 24, SPSS Inc. An IBM Corp. Armonk, NY) program was used for statistical analysis. Continuous variables were expressed by mean ± standard deviation (SD). Categorical variables were expressed by numbers and percentiles. The Kolmogorov-Smirnov test was used to analyze the normal distribution of the data, and the data were found to have a normal distribution. The student t-test was used to compare variables. Pearson correlation analysis was performed to evaluate whether there was a relationship between retinal structure and UPDRS Part III and H&Y scale in IPD patients. A probability value of $p < 0.05$ was considered statistically significant.

Results

The mean age of the patient and control groups was 43.96 ± 4.88 years, 44.53 ± 0.83 years, respectively. The mean duration of the disease in the IPD group was 7.48 ± 5.10 months at the start of the study (range 0–16). The characteristics of the patients and controls, such as gender distribution, IPD treatment distribution, IPD onset side are summarized in Table 1.

Table 1
Baseline characteristics of IPD group and control group.

Parameter	IPD group	Control group	p
Age (Years, Mean ± SD)	43,96 ± 4,88	44,53 ± 0,83	0.661
Gender (M/F)	12/11 (52,2/47,8)	17/13(58,6/41,4)	0.745*
Disease duration (Month, Mean ± SD)	7,48 ± 5,10	-	-
IPD onset side (Right/Left, %)	12/11(52,2/47,8)	-	-
Anti-parkinsonian drugs (L-dopa/Dopa Agonist/Both, %)	7/9/7 (30,4/39,1/30,4)	-	-
Total levodopa daily dose (mg)[a]	150/200/200	-	-
IPD, idiopathic Parkinson's disease; M, male; F, female; SD, standart deviation			
*Chi-square test			
[a] Levodopa equivalent daily dose			

There were no significant differences between the demographic characteristics of the IPD and control groups. (Table 1)

The BCVA, IOP, UPDRS scores, H&Y scores, CMT and RNFL thicknesses (average and all quadrants) values of the IPD patients at all visits are summarized in Table 2. The BCVA, IOP, CMT and RNFL thickness (average and all quadrants) values of the controls at all visits are summarized in Table 3. There was no statistically significant difference in the BCVA and IOP values of the groups during the 2-year follow-up period ($p > 0.05$, $p > 0.05$, respectively)

Table 2

Clinical findings of IPD patients at two-year follow-up. (n = 23)

Parameter	E1	E2	E3	E4	E5
BCVA	0.93 ± 0.08	0.93 ± 0.08	0.92 ± 0.08	0.92 ± 0.09	0.91 ± 0.08
IOP (mm Hg)	14.48 ± 1.59	14.52 ± 1.47	14.57 ± 1.47	14.57 ± 1.53	14.70 ± 1.39
UPDRS part III	23.65 ± 4.94	24.57 ± 5.14	25.74 ± 6.00	27.09 ± 5.83	28.35 ± 6.22
H&Y stage	1.13 ± 0.34	1.22 ± 0.42	1.48 ± 0.59	1.70 ± 0.70	2.00 ± 0.79
CMT (μm)	247.65 ± 8.80	246.96 ± 8.12	246.74 ± 7.84	246.65 ± 7.49	245.61 ± 7.04
RNFL (μm)					
Average	100.09 ± 7.80	98.65 ± 9.72	96.96 ± 8.30	95.65 ± 6.91	94.17 ± 7.91
Superior	122.00 ± 13.53	122.30 ± 15.49	116.87 ± 11.74	115.70 ± 11.62	113.61 ± 17.18
Inferior	130.52 ± 14.43	129.26 ± 15.84	125.74 ± 16.08	125.43 ± 9.37	126.17 ± 16.00
Nasal	76.70 ± 11.60	77.30 ± 11.15	74.04 ± 13.15	74.39 ± 11.42	72.61 ± 9.92
Temporal	69.22 ± 9.66	64.26 ± 9.80	67.83 ± 8.59	65.70 ± 9.47	64.91 ± 7.59

IPD, Idiopatic Parkinson disease; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y stage, Hoehn-Yahr stage; CMT, Central macular thickness; RNFL, Retinal nerve fiber layer; BCVA, best corrected visual aqutiy; IOP, ıntracular pressure; E1, first examination; E2, second examination; E3, third examination; E4, fourth examination, E5, fifth examination

Table 3

Clinical findings of control group at two-year follow-up. (n = 30)

Parameter	E1	E2	E3	E4	E5
BCVA	0.93 ± 0.09	0.92 ± 0.09	0.92 ± 0.08	0.91 ± 0.09	0.91 ± 0.09
IOP (mm Hg)	14.57 ± 1.40	14.57 ± 1.38	14.47 ± 1.61	14.50 ± 1.40	14.77 ± 1.33
CMT (µm)	247.70 ± 8.53	247.03 ± 8.01	246.83 ± 7.80	247.40 ± 7.73	244.83 ± 6.83
RNFL(µm)					
Average	99.47 ± 8.10	98.97 ± 10.23	98.50 ± 7.84	97.67 ± 8.22	98.93 ± 7.56
Superior	122.77 ± 11.61	118.57 ± 10.39	117.90 ± 9.88	119.63 ± 9.26	121.47 ± 8.61
Inferior	129.63 ± 13.06	129.07 ± 15.80	126.27 ± 15.07	126.13 ± 9.03	126.87 ± 16.09
Nasal	75.87 ± 11.44	76.90 ± 10.24	73.97 ± 13.18	74.13 ± 10.42	72.23 ± 10.40
Temporal	67.93 ± 9.51	63.47 ± 10.25	68.13 ± 7.64	64.57 ± 10.33	64.50 ± 7.43

BCVA, best corrected visual aqutiy; IOP, ıntracular pressure; CMT, Central macular thickness; RNFL, Retinal nerve fiber layer; E1, first examination; E2, second examination; E3, third examination; E4, fourth examination, E5, fifth examination

Patients' initial, 6th month, 12th month, 18th month, and 24th -month UPDRS Part III scores were 23.65 ± 4.94, 24.57 ± 5.14, 25.74 ± 6.00, 27.09 ± 5.83, 28.35 ± 6.22, respectively. During follow-up, the increase in UPDRS part III scores was statistically significant ($p < 0.05$) Patients' initial, 6th month, 12th month, 18th month, and 24th -month H&Y scores were 1.17 ± 0.38, 1.17 ± 0.38, 1.48 ± 0.59, 1.70 ± 0.70, and 2.00 ± 0.79, respectively. While there was no significant difference in H&Y scores between the first and second examination, the scores tended to increase in the subsequent controls, and this increase was statistically significant ($p = 0.162$, $p < 0.05$)

Average and superior quadrant RNFL thicknesses were statistically different between the two groups at 24 months and there was no significant difference between other visits ($p = 0.025$, $p = 0.034$, $p > 0.05$, respectively). In addition, there was no statistically significant difference between the visits in terms of RNFL thickness values in the inferior, nasal and temporal quadrants ($p > 0.05$) (Table 4). There was no statistically significant difference in CMT between the two groups during the follow-up period ($p > 0.05$) (Table 4).

Table 4

Comparison of groups at two-year follow-up. (Independent Samples t-test)

Parameter	p (E1)	p (E2)	p (E3)	p (E4)	p (E5)
BCVA	0.717	0.774	0.793	0.738	0.765
IOP (mm Hg)	0.831	0.910	0.820	0.873	0.851
CMT (µm)	0.984	0.973	0.965	0.725	0.712
RNFL(µm)					
Average	0.780	0.910	0.492	0.581	0.025
Superior	0.825	0.299	0.730	0.176	0.034
Inferior	0.816	0.965	0.903	0.785	0.877
Nasal	0.796	0.892	0.983	0.932	0.895
Temporal	0.631	0.777	0.891	0.685	0.843

BCVA, best corrected visual aqutiy; IOP, ıntracular pressure; ; CMT, Central macular thickness; RNFL, Retinal nerve fiber layer; E1, first examination; E2, second examination; E3, third examination; E4, fourth examination, E5, fifth examination

According to Pearson correlation analysis, no significant correlation was found between average RNFL thickness, CMT, UPDRS part III scores and H&Y scale scores in the IPD group ($p > 0.05$) (Table 5).

Table 5
Correlation analysis between UPDRS part III, H&Y scale and average RNFL thickness in IPD patients. (Pearson correlation test)

	Average RNFL thickness									
	E1		E2		E3		E4		E5	
	r	p	r	p	r	p	r	p	r	p
UPDRS										
E1	-0,037	0,867	-0,152	0,489	-0,005	0,983	-0,268	0,215	-0,115	0,600
E2	-0,027	0,901	-0,131	0,550	-0,045	0,838	-0,287	0,184	-0,175	0,425
E3	0,029	0,897	-0,130	0,555	0,009	0,968	-0,238	0,273	-0,156	0,478
E4	0,015	0,947	-0,153	0,485	-0,008	0,970	-0,250	0,250	-0,246	0,257
E5	0,056	0,801	-0,220	0,314	0,050	0,822	-0,375	0,078	-,274	0,205
H&Y										
E1	-0,021	0,923	0,231	0,288	-,491	0,017	-0,314	0,144	-0,238	0,275
E2	0,160	0,467	-0,025	0,910	-0,205	0,348	-0,241	0,269	-0,323	0,132
E3	0,177	0,419	-0,009	0,967	-0,060	0,785	-0,287	0,185	0,037	0,867
E4	0,063	0,775	-0,069	0,753	-0,166	0,449	-0,185	0,399	-0,108	0,625
E5	0,080	0,716	0,023	0,915	-0,178	0,415	-0,244	0,261	-0,160	0,466

UPDRS, Unified Parkinson's Disease Rating Scale; H&Y stage, Hoehn-Yahr stage; RNFL, retinal nerve fiber layer; E1, first examination; E2, second examination; E3, third examination; E4, fourth examination, E5, fifth examination

Discussion

In this study, which aims to evaluate the relationship between IPD progression and RNFL, the average and superior quadrant RNFL thicknesses were significantly thinner at the 24th month in the IPD group compared to the control group.

OCT is a reliable and cost-effective technique used to evaluate RNFL thickness in the optic nerve head. It is often used in the diagnosis and follow-up of neurodegenerative diseases, such as multiple sclerosis, which leads to optic neuritis [15].

In IPD, another neurodegenerative disease that affects the elderly population, there may be difficulties in diagnosis by clinicians, especially due to the cardinal symptoms that do not appear in the early stage. Computed brain tomography or Magnetic Resonance Imaging images are insufficient to distinguish IPD

from other neurodegenerative diseases and diagnosis is generally made by clinical examination. However, it is difficult to distinguish IPD with essential tremor and other types of tremor, which is similar to IPD, in cases where other cardinal symptoms of the disease are not dominant, and patients may receive incorrect treatments [9, 15].

Considering the related literature on OCT, which is seen as a potential candidate for IPD early diagnosis in recent years, the RNFL thickness examined with OCT was found to be reported as decreased in many studies.

Inzelberg et al. reported that RNFL thicknesses in the inferior quadrant in the IPD patients were thinner than in the control group [16]. Moschos et al. reported that RNFL thicknesses in the inferior and temporal quadrants in the IPD patients were thinner than in the control group [17]. Kırbaş et al. found thinning in RNFL values in average and temporal quadrants in newly diagnosed IPD patients [18]. In a study conducted by Altıntaş et al. with 17 IPD patients and 11 controls, where RNFL and macular thickness were evaluated by OCT, macular thickness and RNFL in all quadrants and average RNFL values in the IPD group were found to be thinner than the control group [19]. In a meta-analysis of 13 case-control studies conducted by Yu et al., eyes of 644 IPD patient and 604 healthy controls were examined by OCT, and average RNFL values and RNFL values in the temporal quadrant were found to be thinner in IPD patients compared to the control group [15].

However, in other studies, no significant difference was found between the IPD and control groups in terms of the RNFL thickness examined with OCT. In a study conducted in the U.S., IPD disease and the control group were assessed by OCT, and no significant difference was reported between average RNFL values, despite the decreased macular thickness in the IPD group [20]. In a study conducted in the U.K., 51 IPD patients and 25 healthy controls were evaluated, and no difference was found between macular thickness and RNFL values measured with OCT, despite lower visual acuity and contrast sensitivity in the IPD group [21]. Another study in Germany evaluated macular thickness and retinal layers by OCT in healthy controls and Parkinson's plus and IPD patients. And, no significant difference was found between IPD patients and the control group [22].

When we considered all these studies, we concluded that the different results might depend on the disease stage, the ages of the study participants, the OCT device used, and the fact that many of the studies were cross-sectional. In our study, average RNFL and superior quadrant RNFL thicknesses were found to be thinner in the 24th months in IPD patients compared to the controls. However, the inferior, nasal and temporal quadrants measured with OCT showed a thinning with the disease progression in certain periods, but there was no statistical significance.

It was reported that there was no significant relationship between UPDRS and H&Y scores and RNFL values in the studies that evaluated disease severity and RNFL thicknesses, similar to our study [6, 10, 19].

It has been reported that decreased dopamine levels in the retina in IPD patients may be the cause of retinal degeneration. However, in the study conducted by Şen et al., IPD patients who received and did not receive Levodopa therapy and healthy control groups were evaluated with OCT, and no significant difference was reported in the RNFL values in all groups [23]. In our study, there was no significant relationship between RNFL values in the patients who received Levodopa and dopa agonist as monotherapy. Moreover, non-medicated IPD patients were not included in the study since the patients received treatment during the study.

In the study conducted by Satue et al., where IPD progression and retinal degeneration were evaluated in the similar patients, the IPD patient and control groups were re-evaluated 5 years after the first evaluation with OCT, and macular thickness and RNFL values in all quadrants in the IPD group were found to decrease significantly compared to the control group [24]. However, in a study by Hasanov et al., early-stage IPD patient and healthy control groups were followed up with 6-month intervals at least 3 times by OCT in terms of their RNFL and macular thickness values. There was no significant reduction in the average RNFL and macular thickness values, but a thinning was present in RNFL value only in the superior quadrant in the patient group. In this study, we believe that the short duration of follow-up may be the reason why the results were unrelated [10].

In our study, however, superior quadrant and average RNFL thicknesses were significantly thinner in the 24th months, compared to the groups.

A small number of patients and the shorter observation period are among the limitations of our study. However, in other studies in the literature, the number of patients was not significantly higher than those included in our study. We also believe that our study may be valuable since there are not many studies investigating retinal abnormalities with disease progression.

Conclusions

As a result, we believe that OCT is a potential biomarker in the diagnosis of IPD, especially during the early stages. We also believe that our study may be valuable since there are not many studies investigating retinal abnormalities with disease progression.

However, larger and more comprehensive studies that use OCT for evaluating the relationship between retinal and macular pathologies with neurodegeneration that develops with the disease progression may contribute to understanding these pathologies.

Abbreviations

IPD
Idiopathic Parkinson's disease
BCVA
Best-corrected visual acuity

IOP
Intraocular pressure
CMT
Central macular thickness
RNFL
Retinal nerve fiber layer
OCT
Optical Coherence Tomography
UPDRS Part III
Unified Parkinson's Disease Rating Scale part III
H&Y
Hoehn and Yahr

Declarations

Ethics approval and consent to participate: Patients' written informed consent and the approval of the local ethics committee were obtained for the research. Sakarya University Faculty of Medicine Ethic Committee (Number: 51522473/050.01.04/94)

Consent for Publication: Not applicable

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