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Article *in* International Ophthalmology · May 2018

DOI: 10.1007/s10792-018-0934-y

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ORIGINAL PAPER

Functional and morphological assessment of ocular structures and follow-up of patients with early-stage Parkinson's disease

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Received: 6 March 2018 / Accepted: 21 April 2018

Abstract
Purpose To evaluate and follow-up of functional and morphological changes of the optic nerve and ocular structures prospectively in patients with early-stage Parkinson's disease.
Materials and methods Nineteen patients with a diagnosis of early-stage Parkinson's disease and 19 age-matched healthy controls were included in the study. All participants were examined minimum three times at the intervals of at least 6 month following initial examination. Pattern visually evoked potentials (VEP), contrast sensitivity assessments at photopic conditions, color vision tests with Ishihara cards and full-field visual field tests were performed in addition to measurement of retinal nerve fiber layer (RNFL) thickness of four quadrants (top, bottom, nasal, temporal), central and mean macular thickness and macular volumes.
Results Best corrected visual acuity was observed significantly lower in study group within all three examinations. Contrast sensitivity values of the patient group were significantly lower in all spatial frequencies. P100 wave latency of VEP was significantly longer, and amplitude was lower in patient group; however, significant deterioration was not observed during the follow-up. Although average peripapillary RNFL thickness was not significant between groups, RNFL thickness in the upper quadrant was thinner in the patient group. While there was no difference in terms of mean macular thickness and total macular volume values between the groups initially, a significant decrease occurred in the patient group during the follow-up. During the initial and follow-up process, a significant deterioration in visual field was observed in the patient group.
Conclusion Structural and functional disorders shown as electro-physiologically and morphologically exist in different parts of visual pathways in early-stage Parkinson's disease.

Keywords Parkinson's disease · Contrast sensitivity · Color vision · Visual field analysis · VEP · OCT · RNFL thickness · Macular thickness · Macular volume

This original article has been previously presented in Turkish Ophthalmology Society Meeting in 2016 Antalya, Turkey.

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Introduction

Parkinson's disease (PD) is an age-related neurodegenerative disease that manifests with progressive loss of dopaminergic neurons in the substantia nigra [1].

Published online: 09 May 2018

Apart from motor and non-motor manifestations, visual symptoms are also common and may vary widely from dry eye and reading difficulty, to complex visual hallucinations [2–5]. Such visual symptoms and hallucinations are major causes of morbidity and mortality in PD [6]. Psychophysical, electrophysiological, and morphological evidence demonstrates the presence of structural and functional disruptions at different stages of the visual pathway in PD. In addition, the 'higher' (cortical) visual processes are also affected. Both structural and functional changes develop in the retina and optic nerve in PD. Reduced visual acuity and contrast sensitivity, impaired color vision, retinal nerve fiber layer (RNFL) thinning, reduced macular thickness, altered electrophysiological tests, and visual field and motor perception defects have been reported in patients with PD [1].

The aim of this study was to evaluate and follow functional and morphological changes in the optic nerve and retina in patients with early-stage PD.

Materials and methods

The study was designed as a single-center, controlled, randomized, perspective clinical study. Patients being followed for early-stage PD (Hoehn and Yahr Stage 1 or 2) and age-matched healthy volunteers were included in the study. Patients with high myopia (> -6.0 diopter) or astigmatism (> 3 diopter), glaucoma, dense cataract (Grade 3 or higher on the LOCS III classification), congenital or acquired macular or optic nerve disease, history of any ocular surgery, diabetes mellitus or hypertension were not included. After the initial examination, patients and healthy subjects were examined 3 times at intervals of at least 6 months. All patients underwent best corrected visual acuity (BCVA) measurement using Snellen chart, slit-lamp anterior and posterior segment examination, and IOP measurement using Goldmann applanation tonometry.

Contrast sensitivity was assessed at spatial frequencies ranging from 0.4 to 15 cycles/degree in photopic conditions using the MetroVision (Monopack 3, France) instrument. Color vision was evaluated using Ishihara pseudoisochromatic plates (Optitech Eyecare, Allahabad, India) from a distance of 75 cm at a 300–500 lx artificial lighting with presbyopic correction. Visual field testing was conducted by standard automated perimetry with a white background at 10 cd/m^2 lumination and a 4 mm^2 stimulus size (equivalent to Goldmann perimeter size III target) using a 60° full-field 120 points threshold test (Humphrey Field Analyzer II). Visual field data from subjects with undetectable blind spot, fixation loss, or high rates of false negative or false positive results were not considered reliable and were not included in the analysis. Two ophthalmologists statistically analyzed each visual field output by counting the number of unseen points in the full field and each quadrant, as described in the literature [7, 8].

All subjects underwent pattern visual evoked potential (VEP) testing under standard conditions using the Metrovision (Monopack 3, France) electrophysiology device. An alternating checkerboard pattern was used as the pattern stimulus, and the visual angle was set to 30 min of arc. The screen lumination was 100 cd/m^2, there was 99% contrast between the black and white squares, the pattern alternation speed was 2/s, and the duration of analysis was 300 ms. P100 latency and amplitude values were recorded for each subject.

Optical coherence tomography (OCT) was done using a 3D OCT-2000 (Topcon Inc., Japan). The 6.0 × 6.0 mm, 512 × 128 3D scan mode was used to measure peripapillary RNFL and macular thickness. RNFL thickness, mean macular thickness (MMT), macular volume (MV) and central macular thickness (CMT) were recorded for the total peripapillary area and the four quadrants.

Statistical analysis was performed using Shapiro–Wilk test, *t* test, Wilcoxon test, Mann–Whitney test and Chi-square test. SPSS version 18.0 (Statistical Package for the Social Sciences, IBM, USA) was used for all statistical analyses.

The study was approved by the Ege University Faculty of Medicine ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent forms were obtained from all participants.

Results

The study included 38 eyes of 19 patients (Group 1) being followed between July 2013 and August 2015 in the Ege University Faculty of Medicine, Department of Neurology for early-stage PD (Hoehn and Yahr

Stage 1 or 2) and 38 eyes of 19 age-matched healthy control subjects (Group 2). Mean age of the patients was 54.39 ± 5.71 (range, 44–70) years; mean age of the control group was 55.53 ± 6.48 (range, 42–65) years. Mean follow-up time was 19 ± 8.5 (range, 6–35) months and 15.15 ± 2.7 [12–20] months in the patient and control groups, respectively (Mann–Whitney U test, $p = 0.191$). Disease duration in Parkinson group varied between 3 and 180 months, with a mean of 47.21 ± 41.15 months. All patients were receiving an anti-Parkinson drug (L-DOPA, Selegiline, Rasagiline, Pramipexole, Ropinirole) at initial examination and during follow-up.

Mean BCVA was 0.90 ± 0.14 (range, 0.4–1.0) at initial examination, 0.86 ± 0.19 (range, 0.4–1.0) at the second examination, and 0.85 ± 0.22 (range, 0.4–1.0) at the third examination, declining significantly in study group. The reduction in BCVA was due to cataract formation in 6 eyes of 4 patients, and after excluding these patients from the study group, there were no statistical differences in BCVA in between-group comparisons. Cataract surgery was recommended in 3 eyes of 3 patients, and 2 eyes underwent cataract surgery with improved visual acuity to 1.0 following operation. Within-group and between-group statistical comparisons of BCVA are shown in Table 1.

In the patient group, IOP values at the second and third examinations were significantly higher compared to initial values (t test, $p = 0.006$ and $p < 0.001$, respectively). There was no other significant difference in within-group and between-group comparisons regarding IOP (t test, $p > 0.05$). No changes in color vision or dyschromatopsia were observed during follow-up in the patient or control groups.

Neither group showed any change in contrast sensitivity function as measured with the MetroVision system (t test, $p > 0.05$) in the follow-up period. Contrast sensitivity values in Group 1 were generally lower than those of the control group at all 3 examinations at all spatial frequencies. The detail is given in Tables 2 and 3.

Compared to the control group, the patient group had longer P100 latency (t test, $p < 0.05$) and lower P100 amplitude (t test, $p < 0.05$) at all examinations. Neither group showed within-group differences in P100 latency during follow-up (t test, $p > 0.05$). The patient and control groups' P100 latency and amplitude values are shown in Table 4.

No significant between-group or within-group differences emerged in average peripapillary RNFL thickness (t test, $p > 0.05$). Neither group showed within-group differences when quadrants were analyzed separately (t test, $p > 0.05$). In between-group comparison, only the superior quadrant showed a difference in all three examinations; peripapillary RNFL thickness was significantly greater in the controls than in the PD patients in the first, second and third examinations (t test, $p = 0.012$, $p = 0.016$ and $p = 0.036$, respectively). Total and quadrantal peripapillary RNFL values are shown in Table 5.

No significant differences in CMT and MMT were observed within or between the groups ($p > 0.05$). However, there was a significant difference in MMT of patient group in third examination both in within-group compared to the first and second examinations (t test, $p = 0.035$ and $p = 0.002$, respectively) and between-group comparisons (t test, $p = 0.006$) especially in the inner nasal segment of the macula (t test, $p < 0.001$). The patient and control groups' CMT and MMT values are shown in Table 5. Total MV

Table 1 Statistical comparison of inter- and intragroup values according to BCVA

Intragroup evaluation (p values)						Intergroup evaluation (p values)		
Study group			Control group					
E1–E2	E1–E3	E2–E3	E1–E2	E1–E3	E2–E3	E1	E2	E3
0.036*	0.017*	0.190*	0.324*	0.324*	0.324*	0.985**	0.000**	0.033**

BCVA Best corrected visual acuity, *E1* first examination, *E2* second examination, *E3* third examination

*Wilcoxon test

**Mann–Whitney U test

Table 2 Contrast sensitivity values of both groups in different spatial frequencies

Spatial frequency (cycles per degree)	Mean contrast sensitivity (dB) mean ± SD					
	Study group			Control group		
	E1	E2	E3	E1	E2	E3
0.4	16.11 ± 1.3	16.26 ± 2.3	16.10 ± 2.7	17.08 ± 2.1	17.18 ± 2.1	17.63 ± 2.1
0.8	19.28 ± 1.8	19.55 ± 2.4	19.40 ± 2.4	20.11 ± 1.7	20.16 ± 1.6	20.89 ± 1.7
1.6	20.17 ± 2.9	20.61 ± 3.1	20.70 ± 2.6	21.87 ± 1.6	22.03 ± 1.7	22.42 ± 1.8
3.2	19.68 ± 3.1	19.82 ± 3.9	20.00 ± 3.1	21.92 ± 1.8	22.00 ± 2.1	22.21 ± 1.6
6.4	16.89 ± 4.0	17.66 ± 5.0	17.63 ± 4.4	19.37 ± 2.9	19.66 ± 3.2	20.61 ± 2.8
12.8	10.89 ± 4.9	11.13 ± 4.6	10.93 ± 4.1	12.42 ± 4.2	13.79 ± 3.1	13.39 ± 2.8

E1 First examination, *E2* second examination, *E3* third examination, *SD* standard deviation, *dB* decibel

Table 3 Intragroup and intergroup comparison of contrast sensitivity values of in different spatial frequencies both in study and control groups

Spatial frequency (cycles per degree)	Intragroup evaluation (p values)*						Intergroup evaluation (p values)		
	Study group			Control group					
	E1–E2	E1–E3	E2–E3	E1–E2	E1–E3	E2–E3	E1	E2	E3
0.4	0.749	0.067	0.437	0.755	0.120	0.140	0.040	0.076	0.024
0.8	0.579	0.368	0.317	0.863	0.412	0.324	0.114	0.211	0.009
1.6	0.825	0.795	0.299	0.421	0.065	0.142	0.035	0.014	0.022
3.2	0.616	0.515	0.274	0.772	0.160	0.341	0.016	0.004	0.008
6.4	0.380	0.920	0.139	0.419	0.056	0.054	0.051	0.059	0.012
12.8	0.129	0.443	0.126	0.133	0.244	0.547	0.031	0.08	0.019

E1 First examination, *E2* second examination, *E3* third examination

*t test

Table 4 P100 latency and amplitude values in both groups

	Study group			Control group		
	E1	E2	E3	E1	E2	E3
P100 latency (msec)	113.2 ± 11.5	117.1 ± 15.2	109.3 ± 20.2	102.6 ± 2.9	105.1 ± 7.5	104.04 ± 4.8
P100 amplitude (mV)	7.03 ± 3.7	7.5 ± 4.8	6.8 ± 5.7	8.8 ± 4.2	8.9 ± 3.2	8.7 ± 4.03

msec Millisecond, *mV* Millivolt, *E1* first examination, *E2* second examination, *E3* third examination

measured in the third examination was also significantly less in the patient group compared to the control group (t test, $p = 0.013$).

Reliable visual field test results were obtained in patient and control groups in 25 (65.8%) and 38 (100%) eyes in the first, 22 (57.9%) and 35 (92.1%) eyes in the second, 26 (86.7%) and 38 (100%) eyes in the third examination, respectively. The total number of unseen points in the visual field was significantly higher in all quadrants in the patient group in the first and third examinations (t test, $p = 0.021$ and $p = 0.001$, respectively). There was a significant increase in unseen points in patient group in the third examination when compared with the first and second

Table 5 Peripapillary RNFL thickness, central and mean macular thickness values in study and control groups

Quadrants	Peripapillary RNFL thickness (μm) mean ± SD					
	Study group			Control group		
	E1	E2	E3	E1	E2	E3
Superior	112.97 ± 21.84	113.47 ± 17.25	116.40 ± 15.38	123.32 ± 15.05	122.97 ± 17.69	123.31 ± 12.71
Inferior	118.61 ± 21.58	119.29 ± 17.05	120.00 ± 14.91	119.82 ± 13.92	120.50 ± 13.34	119.73 ± 12.07
Nasal	83.13 ± 19.00	81.89 ± 15.24	81.80 ± 17.14	83.89 ± 13.94	84.39 ± 12.75	85.09 ± 10.65
Temporal	73.89 ± 12.86	72.84 ± 12.31	71.97 ± 11.43	70.32 ± 7.46	72.50 ± 9.01	71.02 ± 14.87
Total	96.89 ± 15.13	96.63 ± 11.73	98.23 ± 10.18	98.63 ± 8.29	97.13 ± 8.51	97.07 ± 7.14
Central macular thickness	219.6 ± 55.5	217.8 ± 53.6	231.4 ± 41.5	225.2 ± 29.2	221.7 ± 35.2	225.6 ± 38.8
Mean macular thickness	278.07 ± 17.9	280.9 ± 18.7	270.7 ± 17.5	279.4 ± 18.4	282.8 ± 8.9	280.9 ± 8.6

RNFL Retinal nerve fiber layer, *μm* MicroMeter, *E1* first examination, *E2* second examination, *E3* third examination, *SD* standard deviation

examinations (*t* test, $p = 0.035$ and $p = 0.027$, respectively) with the greatest deterioration in the superior and nasal quadrants. Within-group and between-group statistical comparisons of numbers of unseen points in the visual field are shown in Table 6.

Discussion

PD is the second most common neurodegenerative disease in developed countries, after Alzheimer's disease. Although it develops as a result of progressive loss of dopaminergic neurons in the substantia nigra, PD is a multisystemic pathology with both motor and non-motor manifestations [9, 10] including visual signs and symptoms due to structural and functional anomalies in the retina, optic nerve, and visual cortex [1].

Numerous studies have demonstrated that PD patients have lower BCVA compared to healthy individuals of the same age [11–13]. However, there are also studies reporting no difference in visual acuity between PD patients and control groups [14–16]. In the present study, PD patients had significantly lower visual acuity than the control group, but cataract development and progression was shown to be mainly responsible for this difference. Similar to our study, Nowacka et al. [13] found that nuclear and posterior subcapsular lens opacities were more frequent among PD patients than control subjects. Oxidative stress,

Table 6 Intragroup and intergroup comparison of total number of unseen points in visual field analysis both in study and control groups

Quadrants	Intragroup evaluation (*p* values)*						Intergroup evaluation (*p* values)		
	Study group			Control group					
	E1–E2	E1–E3	E2–E3	E1–E2	E1–E3	E2–E3	E1	E2	E3
Superior	0.712	0.060	0.551	0.963	0.859	0.964	0.013	0.364	0.000
Inferior	0.981	0.002	0.007	0.318	0.113	0.084	0.077	0.691	0.004
Nasal	0.856	0.007	0.053	0.507	0.127	0.618	0.018	0.304	0.001
Temporal	0.681	0.007	0.048	0.830	0.314	0.165	0.086	0.705	0.003

E1 first examination, *E2* second examination, *E3* third examination

**t* test

which is also an important factor in the pathogenesis of PD, has been implicated in cataract development and has been reported that oxidation of the lens DNA, proteins and lipids causes opacification of the lens [17]. This may explain the increased prevalence of cataract among PD patients. There have been no reports in the literature of cataractogenic side effects from the drugs used in PD treatment.

There are very few large, community-based studies investigating the link between primary open-angle glaucoma and PD. It was postulated that PD patients were at high risk for both normal tension and primary open-angle glaucoma [13]. On the other hand, various studies have reported no differences in IOP between PD patients and control subjects [11, 14, 15, 18–20]. Our results corroborate these studies, as we observed no differences in IOP between PD patients and controls in any of the three examinations and found no signs of glaucomatous optic nerve damage in ophthalmoscopic examination or peripapillary RNFL measurements.

Previous studies have documented glaucoma-like visual field defects in PD patients with no other signs of glaucoma [18, 19]. Apoptosis of retinal ganglion cells death mimics the ganglion cell death that occurs in glaucomatous optic neuropathy, thus causing the glaucoma-like visual field defects seen in such neurodegenerative diseases [21]. In our study, PD patients' visual field results were significantly worse than the control group in the first and third examinations, and as a first in the literature, we documented significant progression of visual field defects during follow-up; however, consistent with Tsironi et al.'s study [18], we found that these defects were not accompanied by RNFL losses. There was no statistically significant relationship between visual field defects and disease stage or laterality.

Numerous studies using various contrast sensitivity charts have demonstrated that the contrast sensitivity of PD patients is reduced at different spatial frequencies [12, 13, 22–24] and the reduction has been shown to be greatest at medium and high spatial frequencies [25, 26]. Reduced contrast sensitivity is associated with low levels of retinal dopamine and treatment with L-dopa results in improved contrast sensitivity at all spatial frequencies [27]. In the present study, we found that contrast sensitivity values of the PD patients were generally lower than those of the control group at all 3 examinations at low, medium, and high spatial frequencies. Comparisons between studies are difficult due to differences between contrast sensitivity tests used in the studies and failure to determine patient-related factors which may influence the test results. We observed no significant changes in contrast sensitivity over the course of follow-up in our study, making ours the first study in the literature in which contrast sensitivity remained stable during follow-up.

Another pathology that has been reported in PD patients is color vision disorders [23, 28, 29]. Dopamine acts as a neurotransmitter in amacrine cells, interplexiform neurons, the neurons of the lateral geniculate nucleus and visual cortex influencing the activity of cones [30, 31]. Red–green color vision defects are more common in PD patients than blue–yellow color vision defects which predominate with aging and retinal diseases [32, 33]. We did not detect significant red–green color vision defects in our PD patients or controls, which is in concordance with the results of other studies that evaluated color vision with Ishihara pseudoisochromatic cards [11, 16]. Ours is the first study in the literature to follow color vision in PD patients. The fact that all of our patients had early-stage PD and were taking anti-Parkinson drugs may explain why we did not detect any color vision dysfunction during follow-up. However, we did not use sensitive tests like the FM and D-15, which may also explain the difference between our results and those of other studies.

Longer VEP latency and reduced amplitude have been observed in PD patients [34]. Some studies have shown no significant difference between PD patients and control groups in terms of VEP latency [35]. There are also studies reporting that dopaminergic drugs eliminated the VEP delay [36]. In our study, PD patients exhibited longer VEP latency and smaller amplitudes at all three examinations but showed no significant changes in P100 latency and amplitude over the course of follow-up.

Many studies reported RNFL thinning in PD patients [11, 37–42], though there are also studies reporting no change in RNFL thickness [13, 18, 43–45]. These discrepancies between studies may be due to differences in the age of patients studied, disease stage, and OCT device used. We found no significant difference in peripapillary RNFL thickness between the PD patients and controls. Separate analysis of the peripapillary quadrants in our study revealed that RNFL thickness in the superior

hemisphere was significantly thinner in the patient group at all three examinations. Reduced MV in PD patients has been documented in the literature [11, 41, 45, 46], and this decrease in macular thickness is reported to be predominantly from the inner retinal layers [18, 41, 47, 48]. Although we did not observe a significant difference in CMT, the patient group had significantly lower MMT and total MV values in the third examination, and the reduction in MMT was mainly in the inner and outer nasal macular segments. We were unable to detect any correlation between MV and disease stage, however, signs of RNFL and macular thinning may be useful in detecting PD in its early stages and evaluating disease progression and treatment response.

In brief, there are structural and functional defects in various stages of the visual pathway in PD. Awareness of these changes is beneficial both in monitoring progression and in reducing morbidity of patients with PD.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Written informed consent was obtained from the subjects, and the study was conducted according to the tenets of the Declaration of Helsinki.

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