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Research Article

Evaluation of Visual Evoked Potential and Optical Coherence Tomography Results in Idiopathic Parkinson's Disease Patients

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Abstract

Objectives: This study evaluates Visual Evoked Potential (VEP) and Optical Coherence Tomography (OCT) in Idiopathic Parkinson's Disease (PD) Patients; analyzes the relation between the disease's severity and such values, and investigates the presence of interocular asymmetry in patients with one-sided dominance.

Methods: 40 eyes of 20 PD patients at various stages were evaluated. The disease's severity was measured via UPDRS (Unified Parkinson's Disease Rating Scale) and Hoehn&Yahr (H&Y) scales.

Results: There were 21 (52%) eyes with a pathological P100 latency. P100 latency prolonged as the H&Y staging went up; however, it was not statistically significant. Retinal nerve fiber layer (RNFL) thickness was normal in 70% and retinal thinning was found in 25% of the eyes. The most thinning was observed in the lower and upper quadrant, respectively. Central macular thickness decreased in 62.5% and macular volume decreased in 70% of the eyes. The difference in average RNFL thickness was higher in patients with motor involvement on the left (p=0.044).

Conclusion: It was observed that P100 latency prolonged in parallel with the progression of the disease stage, and average RNFL thickness increased in advanced stages while the central macular thickness and volume decreased. P100 latency can be measured in addition to UPDRS for evaluating the PD's severity.

Keywords: Optical coherence tomography, parkinson's disease, retinal nerve fiber thickness, visual evoked potential

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Visual findings are of great importance among the non-motor symptoms of PD. Decrease in visual acuity, color vision and contrast sensitivity might be observed. Dysfunction is associated with both higher cortical function disorders and the retinal structure.[1]

Dopamine is the major catecholamine found in retina and is possible transmitter for amacrine and/or inter-plexiform cells.[2] Biochemical and pharmacological studies showed that the dopamine receptors in the retina are the same as the ones in the brain.[3, 4] Dopaminergic dysfunction in PD may be observed not only in the basal ganglions but in the retina as well and it is notable at horizontal, amacrine, bipolar and ganglion cell levels.

VEPs are the electric signals occurring in the brain in response to a visual stimulus. Its most prominent component is the P100 wave that occurs around 100 ms in normal people. VEP latency is read as the peak latency of the P100 wave and this value is under 115 ms in normal people below the age of 60. VEP is a sensitive and reliable test in the evaluation of macular and optical nerve functions.[5]

Retinal dopamine deficiency is considered as the main mechanism of visual dysfunction in PD.[6] Dopaminergic deficiency is the cause of latency delays in VEP and can be normalized through L-Dopa treatment.[7] The improvement in Parkinson's symptoms after 3 months of L-Dopa treatment was associated with the improvement in the P100 latency.[6]

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OCT is an imaging method for obtaining high-resolution cross-sectional images in biological tissues, and allows non-invasive imaging of the retinal nerve fiber layer (RNFL) affected due to retinal ganglion cell damage in PD patients. Displaying structural changes in case of axonal damage, RNFL enables in vivo detection of neurodegeneration and RNFL thickness measurement follow-ups are on the agenda in neurodegenerative diseases characterized by neuron damage.[8]

In PD patients, functional and structural changes occur in retina. While the functional changes can be measured via VEP, the structural changes can be evaluated via OCT, which is an imaging technique that allows high-resolution cross-sectional imaging of the biological tissues.

Methods

A total of 20 patients from Movement Disorders outpatient clinic, 13 men and 7 women, with a mean age of 63.5±10.6 (min: 43-max: 82), matching the Idiopathic PD diagnosis criteria, falling between stage 1-4 according to the H&Y scale were included in this study. Thus, the VEP and OCT evaluations were performed on 40 eyes. Questionnaires were applied for Parkinson patients. The staging was performed according to the modified H&Y scale. Clinical severity level was evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS). UPDRS evaluates the patients according to 4 clinical characteristics (total 183 points) including motor examination (total 92 points), activities of daily living (total 52 points), mentation-behavior-mood (total 16 points) and complications of therapy (total 23 points).[1]

Anamneses, backgrounds and family histories of all patients were analyzed; their routine physical and neurological examinations were performed by two neurologists. Initial findings and symptoms, current clinical and side findings were determined. H&Y stage and UPDRS score were calculated.

In accordance with the exclusion criteria, Stage 5 patients were excluded as they would experience compliance and application problems during tests due to the severity of their clinical condition; patients with insufficient visual acuity (not going over 8/10 with correction) or with opacities blocking vision (cataracts etc.), glaucoma, retinal diseases, history of intraocular surgery or laser applications, neurological diseases other than PD that could affect the retina, diabetes mellitus, severe hypertension or cooperation difficulty were also excluded from the study.

The L-Dopa preparations the patients were taking were continued with the same dosage. All subjects gave their written informed consent and the procedure, approved by the local Ethics Committee with the protocol number of 2017/1654 was in accordance with the Ethical standards established in the Declaration of Helsinki.

VEP measurements were taken at the Neurology Clinic Electroneurophysiology Laboratory, in a half-dark room with sound insulation. A Medelec Synergy® brand EMG-VEP device was used. Measurements were taken from both eyes separately, without using miotic or mydriatic eye drops, by correcting the visual impairments and closing the other eye. The patient was 1 meter away from the screen providing the stimulus. The patient was asked to look at a red fixation point in the middle of the screen. The visual stimulus was reflected on a TV monitor and it was in form of a checkerboard reversal pattern where the 2 contrasts switched places per second. The active electrode was in Oz position and the reference electrode was in midfrontal position. VEP response consisted of 3 wave peaks with negative, positive and again negative poles with latency times of 75, 100 and 145 ms. The peak latency and amplitude of each average wave were measured and response changes in the latency and amplitude of the 100 wave, which was the first positive wavelength, were obtained. VEP P100 latency and VEP N75 P100 amplitude parameters were evaluated. Latency was measured in milliseconds and amplitude was measured in microvolts. During the evaluation of the VEP measurements from a patient, both eyes were evaluated together. P100 latency >117 ms in women and P100 latency >120 ms in men were considered as prolonged latency; if the latency was within normal range and there was a difference over 6 ms between the two eyes, the eye with a prolonged latency was considered as pathological. Amplitudes below 4μV were considered as decreased.

OCT imaging was performed without the need for pupil dilation at the Eye Diseases outpatient clinic of the Hospital. CARL ZEISS Cirrus 4000 HD® brand OCT device was used. For all eyes, the average nerve thicknesses and nerve fiber thicknesses pertaining to the upper, lower, nasal and temporal quadrants were measured in microns. These were compared to the normative database in accordance with the ages of the patients and displayed in gray, white, green, yellow and red color codes. The average central macular thickness was measured in microns and the central macular volume was measured in cubic millimeters. These were also compared to the same database in accordance with the ages of the patients and displayed in the same color codes.

Statistical Analysis

Descriptive data were presented in either n (%) or average ± standard deviation, whichever was appropriate. Fisher Test was used in the comparison of the categorical data;

one-way Anova Test was used in the comparison of measurable data and Pearson Correlation Analysis was used in the analysis of the measurement correlations. P<0.05 was accepted as the value for statistical significance. The analyses were performed on IBM SPSS program version 15.

Results

A total of 20 patients, 7 women and 13 men, were admitted to the study. The mean age of the study group is 63.5±10.6'dir (Table 1).

OCT and VEP data were evaluated in accordance with the reference values stated in the guidelines. There were 21 (52%) eyes with a pathological P100 latency. Evaluation of the RNFL thicknesses revealed that there was retinal thinning in 10 (25%) eyes on average. Thinning was most frequently observed in the lower quadrant. The detailed data from the OCT and VEP values in accordance with the reference values are given in Table 2.

When the RNFL thickness, macular thickness and volume defect percentage distribution according to quadrants were analyzed, it was observed that the defect ratio was higher in the lower quadrant of the RNFL compared to the other quadrants. The macular thickness and volume defect rates were also higher than that of the RNFL thickness defects.

While the P100 latency prolonged in parallel with the progression of the disease stage, it was not statistically significant. It was observed that while the average RNFL thickness increased, the central macular thickness and volume decreased in advanced stages (Table 3).

The RNFL thickness on the side where there was no motor involvement was deducted from the RNFL thickness on the side with motor involvement in order to find out whether the retinal thinning was greater on the latter, and the difference was calculated. The aim was to find out if the side with motor involvement was affected more. The negative values indicate the thinning. The difference in the average RNFL thickness was significantly higher in patients with motor involvement on the left side (p=0.044) (Table 4).

The analysis of the VEP and OCT data according to the eye side revealed no statistically significant difference between the side and the P100 latency and amplitude, average RNFL and upper, lower, nasal quadrant and temporal quadrant thicknesses, central macular thickness and volume (Table 5).

When the OCT results were evaluated via the defect percentage method; the advanced central macular thickness defect percentage on the left eye side (the thinnest 1% of measurements) was higher compared to the right side (p=0.035). No statistically significant correlation was found between the other OCT results and the eye side.

Table 1. Demographic and descriptive clinical characteristics of the study group

Sex, n (%)	
Female	7 (35.0)
Male	13 (65.0)
Age (Mean±SD)	63.5±10.6
HY Stages, n (%)	
Stage 1	7 (35.0)
Stage 2	5 (25.0)
Stage 3	6 (30.0)
Stage 4	2 (10.0)
PD duration (Mean±SD)	4.4±3.7

SD: Standard deviation.

Table 2. Evaluation of the distribution of OCT and VEP values in accordance with the reference values

	n (%)
P100 latency	
Pathological	21 (52.5)
Normal	19 (47.5)
P100 amplitude	
Decreased	5 (12.5)
Normal	35 (87.5)
RNFL mean thickness	
Thickened	2 (5.0)
Normal	28 (70.0)
Thinned	10 (25.0)
RNFL superior quadrant	
Thickened	2 (5.0)
Normal	28 (70.0)
Thinned	10 (25.0)
RNFL inferior quadrant	
Thickened	6 (15.0)
Normal	23 (57.5)
Thinned	11 (27.5)
RNFL nasal quadrant	
Thickened	3 (7.5)
Normal	36 (90.0)
Thinned	1 (2.5)
RNFL temporal quadrant	
Thickened	2 (5.0)
Normal	33 (82.5)
Thinned	5 (12.5)
Macular thickness	
Thickened	1 (2.5)
Normal	14 (35.0)
Thinned	25 (62.5)
Central macular volume	
Above average	12 (30.0)
Below avarage	28 (70.0)

Table 3. Analysis of OCT and VEP data in accordance with disease stages

	Stage 1 Mean±SD	Stage 2 Mean±SD	Stage 3 Mean±SD	Stage 4 Mean±SD	p[a]
P100 latency(ms)	115.5±6.8	118.0±9.7	121.4±6.9	124.8±4.0	0.093
P100 amplitude (μV)	5.9±2.5	6.5±2.7	6.2±2.0	5.2±1.9	0.804
RNFL mean thickness (μm)	81.1±13.9	82.1±13.6	88.2±23.6	93.3±5.5	0.511
RNFL superior quadrant (μm)	99.5±24.9	102.8±19.8	98.9±44.2	111.5±8.9	0.897
RNFL inferior quadrant (μm)	104.4±21.2	105.4±17.7	118.5±31.3	125.5±10.1	0.234
RNFL nasal quadrant(μm)	65.6±11.5	56.6±7.2	68.6±14.5	73.0±12.7	0.060
RNFL temporal quadrant (μm)	56.2±10.9	63.5±14.7	67.2±19.0	63.0±7.3	0.293
Macular thickness (μm)	248.6±26.5	223.9±70.8	224.0±69.1	198.8±69.6	0.428
Macular volume (mm^3)	9.9±0.6	9.5±0.6	9.7±1.0	9.3±0.6	0.437

Table 4. Analysis of the difference in retinal thicknesses between eyes according to the side displaying prominent motor symptoms

	PD Dominant side		p[a]
	Right Mean±SD	Left Mean±SD	
ΔP100 latency (ms)	-0.2±2.2	-1.0±2.1	0.360
ΔRNFL mean thickness (μm)	4.8±12.1	-4.6±7.1	0.044
ΔRNFL superior quadrant (μm)	3.7±24.9	-.3±21.8	0.711
ΔRNFL inferior quadrant (μm)	9.3±19.3	-7.7±18.5	0.059
ΔRNFL nasal quadrant (μm)	9.0±9.9	-3.0±16.7	0.074
ΔRNFL temporal quadrant (μm)	-1.0±20.5	-3.9±10.2	0.683

[a]t test in independent groups.

Table 5. Evaluation of the VEP and OCT results according to the eye side

	Side		p[a]
	Right Mean±SD	Left Mean±SD	
P100 latency (ms)	118.6±7.3	119.0±8.6	0.890
P100 amplitude (μV)	6.3±2.3	5.8±2.3	0.518
RNFL mean thickness (μm)	87.1±15.9	82.4±17.9	0.386
RNFL superior quadrant (μm)	102.3±25.5	100.5±33.7	0.850
RNFL inferior quadrant(μm)	115.2±22.9	106.8±24.6	0.268
RNFL nasal quadrant (μm)	67.9±12.1	62.2±12.5	0.152
RNFL temporal quadrant (μm)	62.9±16.1	61.2±13.4	0.719
Macular thickness (μm)	247.0±24.9	213.2±75.3	0.064
Macular Volume (mm^3)	9.7±0.7	9.6±0.8	0.567

SD: Standard Deviation; [a]t test in independent groups.

Discussion

Electrophysiological and morphological changes occur in the retina in PD patients.[1] The integrity of the retinal ganglion cell nerve fiber is evaluated by measuring the RNFL thickness via OCT.[9] In some studies, retinal thinning, delay in VEP latencies and amplitude decrease in pattern electroretinography (PERG) were detected in PD patients. These results support the hypothesis suggesting that dopaminergic deficiency in retina can cause structural and functional changes.[1, 6, 10] However, there is a limited number of studies evaluating visual functions and OCT measurements at the same time.[11, 12]

In our study, the average P100 latency for both sexes was detected as 118.8±7.8 ms: average P100 latency in women was 117.1±6.4 ms while it was 119.7±8.5 ms in men. P100 latency was prolonged in 52.5% of the patients. In VEP analyses in studies on PD patients since the first study by Bodis, P100 latency has been found pathological.[6, 13, 14]

In our study, average VEP amplitude was detected as 6.3±2.3 μV and this average was normal. Amplitude was found to be decreased in 12.5% of the patients. Prolonged P100 latency suggests the functional involvement of the retina. Decreased P100 amplitude, however, can be evaluated as suggestive of axonal involvement. Axons extending from ganglion cells continue towards the brain through the optic nerve.[15] Thus, decrease in amplitude due to axon involvement can be observed in PD patients. The reason behind the amplitude decrease can be explained by the dopamine treatment the patients were receiving.[16]

The P100 latency prolonged in parallel with the disease stage, however this was not statistically significant (p=0.093). A strong positive correlation was found between the UPDRS and P100 latency (p=0.001). In the study by Altıntaş et al.[12] there was no significant difference between the P100 latency value and the control group value; however, they found a significant correlation between the funtional retinal changes and the PD stage.

In our study, the average RNFL value was detected as 84.7±16.9 μm. Our values were compared according to the database of Carl Zeiss Cirrus 4000 HD OCT device and RNFL thinning was detected in 25% of the patients. Although the average RNFL value decreased, RNFL thickness in 70% of the patients were within normal range compared to the database of the Cirrus HD-OCT device and this result

showed similarity with other studies. Peripapillary RNFL thinning in PD patients was first detected in 10 patients by Inzelberg et al.[17] in 2004. Peripapillary RNFL represents the axons of ganglion cells. While thinning was detected similarly in some other studies,[11, 13, 19, 21, 29] RNFL thinning was not detected in some and the average thickness was found out to be normal.[21, 22]

The most thinning was detected in the inferior (27.5%) and superior (25%) quadrants. In the study by Kaur et al.[16] significant decrease in RNFL thickness was detected in the upper and temporal quadrants of the patients. There was no difference between the patients and the control group in nasal and lower quadrants. In the study by Garica et al.[15] RNFL thickness decreased in all quadrants except for the nasal quadrant. Bodis-Wollner et al.,[6] Archibald et al.,[1] Kirbas et al.[10] detected thinning especially in the temporal quadrant. In all studies, thinning was detected either in all quadrants or specific quadrants. This shows that there is no quadrant preference in PD and it can be interpreted as there is no intraocular asymmetry. A new meta-analysis showed generalized RNFL thinning in all quadrants.[22]

The central macular thickness in our patients was 230.1±57.9 µm and thinning was 62.5%; the average central macular volume was 9.7±0.7 mm^3 and thinning was observed in 70% of the patients. Foveal thickness was not evaluated. No difference in average macular thickness was found in the study by Kaur et al.[16] no significant difference in macular volume was found between PD patients and control group. In the study by Garcia et al.[15] the thickness of the fovea in the center of the macula was evaluated rather than the central macular thickness and thinning was detected. In the study by Altıntaş et al.[12] thinning was detected in all quadrants of the macula except for fovea in PD patients. Thinning in the average macular volume in PD patients was significantly more compared to the control group. In recent morphological and microvascular studies by Miri et al.[11] on human retina in PD, fovea was stated as the sensitive spot. In our study, the thinning in the macular thickness and volume detected in most of the patients was found similar to the literature. This result supports the theory of alpha-synuclein's effect on the non-DA (nondopaminergic) neurons in the macular region.

Studies suggest that in PD, the retina is affected in parallel with different stages and severity of the disease. Accordingly, many studies analyzed the retina using H&Y score and some other severity-related ratings to evaluate the severity of PD. While there was correlation in some studies, none was found in others.[12, 15, 21, 25] In our study, when the OCT data according to the Hoehn&Yahr stages were analyzed, no statistically significant difference was found between the disease stage and average RNFL, upper, lower, nasal and temporal quadrant thicknesses, central macular thickness and volume. There was no statistically significant difference between UPDRS and the average RNFL, upper, lower, nasal and temporal quadrant thicknesses, central macular thickness and volume.

In our study, when the correlation between age, PD duration, OCT and VEP data was analyzed for the right eye; there was a strong negative correlation between age and average RNFL and RNFL upper quadrant data; a moderate negative correlation between age and RNFL lower quadrant and RNFL temporal quadrant data. A strong negative correlation was found between age and central macular volume. When the age, PDD duration, OCT, VEP data correlation was evaluated for the left eye; there was a moderate negative correlation between age and RNFL temporal quadrant, and a strong negative correlation between age and all other quadrants and average RNFL. There was a moderate positive correlation between PDD duration and RNFL temporal quadrant. There was no correlation between PDD duration and structural changes in the study by Garcia et al.[18] Age and PDD duration was not found in correlation with retinal thinning and functional changes in the study by Cubo et al.[25]

In our study, the difference in the average RNFL thickness was significantly higher in patients with motor involvement on the left side (p=0.044), which suggested interocular asymmetry. In the study by Cubo et al.[25] the macular volume, internal nasal ring thickness, external upper ring thickness, external temporal ring thickness were significantly higher in patients with motor involvement on the left side. This finding is suggestive of interocular asymmetry in patients with left motor dominance. In the study by Bodis Wollner et al.[6] the correlation between the right and left eye of the same patient was not significant. There were differences between patients both in early stages and progressive stages. Visual involvement asymmetry according to the side the symptoms are dominant in has not been evaluated much.

When the correlation between our OCT and VEP data was analyzed, no statistically significant correlation was detected. Garcia et al.[15] stated a correlation between VEP and OCT evaluations. The reason why there was no correlation in our study can be explained by the significant decrease in RNFL thickness due to the dopamine treatment the patients were receiving.

In our IPD patients, 52% of the P100 latency was pathologic in both men and women. P100 latency prolonged as the Hoehn&Yahr stage progressed. This result was not statistically significant. There was a strong positive correlation

between UDPRS and P100 latency. When we evaluated the retinal thickness via OCT, RNFL thickness was normal in 70% of the eyes. There was no correlation between Hoehn&Yahr staging or UPDRS. The most thinning among pathological RNFL thicknesses was observed in the lower quadrant and upper quadrant, respectively. Central macular thickness decreased in 62.5%, macular volume decreased in 70% of the eyes. While the average RNFL thickness increased, the central macular thickness and volume decreased in advanced stages, but this was not statistically significant. The lack of significant decrease in the RNFL thickness can be explained by the dopamine treatment patients underwent. The decrease in the central macular thickness and volume can be explained by the prominent effect of alpha-synuclein on non-DA neurons in retina in PD. Several studies suggest that the foveal region is the most sensitive region and the earliest involvement is observed there. Foveal region thickness was not analyzed in our study.

Conclusion

In addition to UPDRS, P100 latency and VEP can also be used in the evaluation of PD. Rather than RFNL thickness, only the macular thickness and foveal thickness, if possible, can be measured. These suggestions we put forward should be supported by more extensive studies. Further studies involving broader and more homogenous groups are required.

Disclosures

Ethics Committee Approval: All subjects gave their written informed consent and the procedure, approved by the local Ethics Committee with the protocol number of 2017/1654 was in accordance with the ethical standards established in the Declaration of Helsink.

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