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Research Article

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Evaluation of the Visual Pathway in Parkinson's Disease Patients

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Abstract

Objective: This study aimed to evaluate the visual evoked potentials (VEP) and optical coherence tomography (OCT) as a diagnostic biomarker in Parkinson's disease (PD) patients.

Patients and Methods: Forty-seven PD patients were distributed to two groups: Group 1- included 22 newly diagnosed drug naïve PD patients. Group 2- included 25 PD patients receiving antiparkinsonian drugs. Another 20 age and sex-matched healthy subjects were recruited and served as a control group (Group 3). All participants were subjected to full medical history, general and neurological examination. All participants underwent a full neuro-ophthalmologic examination, OCT, and VEP.

Results: The VEP assessment revealed that the p100 latency was significantly delayed in patients' groups in comparison to healthy subjects ($p < 0.0001$). Also, the p100 amplitude was significantly diminished in patients' groups in comparison to healthy subjects ($p < 0.0001$). These parameters showed statistically significant correlations with both disease duration and severity. There was a significant reduction in both average and quadrant Retinal Nerve Fiber Layer (RNFL) thickness ($p < 0.0001$) in PD patients compared to healthy subjects, with more affection of group 2. Decreased average RNFL thickness was correlated to PD duration and severity. In PD patients both delayed P100 Latency and decreased amplitude were in a statistically significant correlation with decreased average RNFL thickness.

Conclusion: Our results indicate PD patients either drug naïve or medicated show functional and morphological changes in the visual pathway, these changes represent a new biomarker for follow up of PD progression.

Keywords

Parkinson's disease, Visual evoked potential, Optic coherence tomography, Retinal nerve fibre layer, Visual pathway

Introduction

Parkinson's Disease (PD) is the most frequent cause of Parkinsonism and is estimated to affect about nine million patients by the year 2030 [1]. Patients with PD experience a broad variety of non-motor symptoms (NMSs) that manifest as cognitive, neuropsychiatric, autonomic and sensory disorders; which worsen with the disease progression and constitute main determinants of their loss of independence [2].

Most PD disease patients had at least one visual symptom including; reading difficulties, sometimes with diplopia, disturbances of complex visual functions such as facial recognition, visuospatial orientation and visual hallucinations [3]. Retinal dopamine deficiency was proposed as the main underlying cause of these visual symptoms in PD, however; the precise underlying mechanisms are still not well understood [4].

Aim of the Study

This study aimed to evaluate the visual evoked potentials (VEP) and optical coherence tomography (OCT) as a diagnostic biomarker in PD.

Patients and Methods

This cross-sectional study was conducted at Tanta university hospitals, Egypt where 47 PD patients diagnosed according to the United Kingdom Parkinson's disease Society Brain Bank diagnostic criteria [5]. They were recruited from the 1st of March 2017 to the 28th of February 2018. PD stages were evaluated by the Hoehn and Yahr scale [6].

Patients with Parkinson plus syndromes, secondary Parkinsonism, other neurological disorder or endocrinal disorder were excluded from our study. Patients with diabetes mellitus, patients known to be suffering glaucomatous media opacity interfering with good quality of images, intraocular surgery, coincidental retinal pathology as myopic choroidal neovascularization, patients suffering age related macular degeneration, retinal vein occlusion, patients received other lines of treatment like laser photocoagulation, intravitreal injection of triamcinolone or other anti VEGF (vascular endothelial growth factor) agents, were excluded from the this study.

PD Patients were classified into two groups: Group 1; included 22 newly diagnosed drug naïve PD patients. Group 2; included 25 PD patients receiving antiparkinsonian drugs. Another 20 age and sex matched healthy subjects were recruited and served as control group (Group 3).

All participant were subjected to the following: full medical history, general and neurological examination, laboratory studies including fasting and postprandial blood glucose level, serum electrolytes, renal function test, liver function test, thyroid hormonal profile, and neuroimaging studies either CT and/or MRI brain if needed.

All participants underwent a full neuro-ophthalmologic examination, including clinical history, best-corrected visual acuity, biomicroscopy of the anterior segment using a slit lamp,Goldmann applanation tonometry®, and ophthalmoscopy of the posterior segment. Optic coherence tomography (OCT) with Ziess Cirrus 4000 spectral domain OCT®. It is Non-invasive method that allows imaging of the retinal nerve fiber layer (RNFL), a structure which contains ganglion cell axons that form the optic nerves, chiasm, and optic tracts.

Visual evoked potential was done by Nicolet Viking Quest EMG / NCS / EP System® to quantify functional integrity of the optic pathways [7]. Pattern-reversal VEP was recorded following International Society of Clinical Electrophysiology of Vision (ISCEV) methods last updated in 2016 [7]. The active electrode was placed over the occipital cortex, with a reference electrode at a nonvisual area, and a ground electrode over the mastoid bone. Dark-and-white checkerboard of equal size was presented as pattern reversal generated on a screen at a distance about 50 cm. Check size was 60 of retinal arc, and contrast ratio was 0.95. They were filtered with cutoff frequencies of 0.5 and 1 Hz. The latencies of N75, P100, N145, and peak-to-peak amplitudes were measured.

A signed informed consent was obtained from all participants and their first-degree relatives. The study protocol was approved by the ethical committee in Tanta University, Egypt, under the code number 3277/12/16 on December 2016.

Statistical Analysis

The collected data were organized, tabulated, and statistically analyzed using SPSS software statistical computer package version 16. For quantitative data, the range in addition to mean and the standard deviation was calculated, and the Pearson correlation equation was used. Significance was adopted at $p < 0.05$ for the interpretation of results of tests of significance.

Table 1: Demographic data (age, duration, sex distribution and Hoehn and Yahr scale) of the studied groups.

		Group 1	Group 2	Group 3	P- value
Age in years (M ± SD)		54.8 ± 6.52	59 ± 3.76	57.2 ± 3.76	0.13
Sex	Male	15 (68%)	18 (72%)	14 (70%)	0.99
	Female	7 (32%)	7 (28%)	6(30%)	
Disease duration (months)		7.1 ± 2.28	43.1 ± 12.25	-	< 0.0001*
Hoehn and Yahr scale	Stage 1	19 (86%)	0 (0%)	-	0.0001*
	Stage 2	3 (14%)	5 (20%)	-	
	Stage 3	0 (0%)	14 (56%)	-	
	Stage 4	0 (0%)	6 (24%)	-	
BMI (M ± SD)		25.5 ± 3.2	25.3 ± 2.91	25.06 ± 3.23	0.44

BMI (Body Mass Index)

Results

The study included 47 PD patients and 20 healthy subjects as a control group. There were no statistically significant differences between the three groups regarding age, sex or Body Mass Index (BMI) as shown in table 1.

Group (1) included 22 drug naïve PD patients, according to Hoehn and Yahr scale; 19 patients were in the first stage while the other 3 patients were in the second stage, those patients have a duration of illness (7.1 ± 2.28) months. On the other hand, group (2) included 25 PD patients already receiving antiparkinsonian medications. According to Hoehn and Yahr scale; 5 patients were in the second stage, 14 patients were in the third stage, while the other 6 patients were in

stage four, and those patients had a duration of illness (43.1 ± 12.25) months. The results showed that there were significant differences among the patients' groups regarding severity of disease measured by Hoehn and Yahr scale and duration of illness as ($p < 0.05$).

There were statistically significant differences among the studied groups regarding the VEP parameters (N75 Latency, P100Latency, N145 Latency, and P100 Amplitude) as demonstrated in table 2. Figure 1 showed delayed P100, N75 and N145 latencies, with decreased P100 amplitudes of a female patient in group 2. Also these parameters (delayed N75, N145 and P100 Latencies and decreased P100 amplitudes) showed statistically significant correlations with both disease duration and stage in both patients groups (Table 3).

Table 2: N75 latency, P100 latency, N145 latency and P100 amplitude mean values in studied population.

1.	Group 1	Group 2	Group 3	p- value
N75 latency (ms)				
Right eye	70.5 ± 1.08	73.9 ± 1.37	65.2 ± 2.34	< 0.0001*
Left eye	71.1 ± 0.87	73.42 ± 1.44	64.85 ± 2.23	< 0.0001*
P100 latency (ms)				
Right eye	102.3 ± 1.63	116.3 ± 2.13	96.3 ± 1.88	< 0.0001*
Left eye	103.3 ± 1.63	116.3 ± 1.60	95.6 ± 1.83	< 0.0001*
N145 latency (ms)				
Right eye	144.9 ± 0.99	150 ± 1.49	142.3 ± 150	< 0.0001*
Left eye	144.7 ± 0.67	149.9 ± 1.37	142 ± 0.99	< 0.0001*
P100 amplitude (uv)				
Right eye	5.27 ± 0.09	4.28 ± 0.15	5.6 ± 0.16	< 0.0001*
Left eye	5.23 ± 0.11	4.25 ± 0.12	5.64 ± 0.11	< 0.0001*

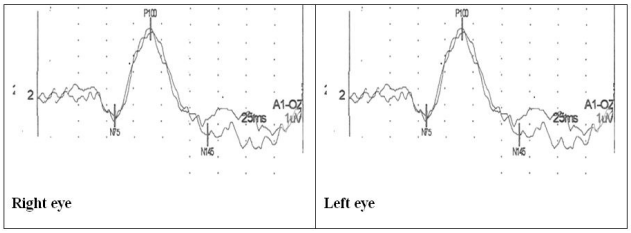

Figure 1: This figure showed delayed P100, N75 and N145 latencies and decreased P100 amplitudes of both eyes (left eye affected more than the right one) female patient sixty-three years old with onset of disease for three years presented by motor manifestation affecting the right and left side of the body (more on right side) and has disease severity (stage 2 Hoehn & Yahr).

There was a significant reduction in average RNFL in PD patients compared with the healthy controls as demonstrated in figure 2 (OCT of the parkinsonian patient in group 2). Moreover, the further analysis provided evidence that there were significant differences in mean values of RNFL thickness between PD patients and control group in superior, inferior, nasal, and temporal quadrants, as showed in table 4.

Our results showed that there was a statistically significant negative correlation between the severity and duration of the disease and the decrease in average RNFL thickness, temporal, nasal, superior, and inferior RNFL thickness (Table 5).

In PD patients both delayed P100 Latency and decreased amplitude showed statistically significant correlations with decreased average RNFL thickness and RNFL thickness of different quadrants as shown in table 6.

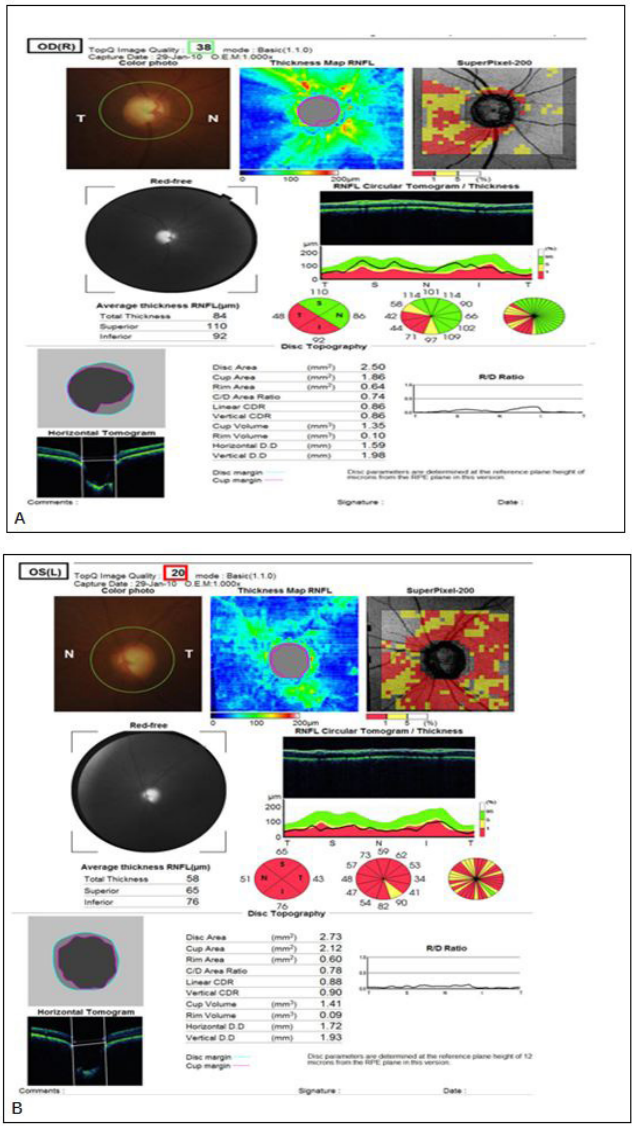

Figure 2: OCT of Parkinson's disease male patient aged 65 years old on antiparkinsonian medication. Right eye (A) shows thinning of inferior and temporal quadrants. While the left eye (B) shows RNFL thinning of all quadrants.

Table 3: Correlation between severity of the disease and visual evoked potentials results and both patients groups.

	Severity (H and Y scale)		Duration of the disease	
	R	***P***	***r***	***P***
N75 latency (ms)	0.90	< 0.0001*	0.80	< 0.0001*
P100 latency (ms)	0.92	< 0.0001*	0.85	< 0.0001*
N145 latency (ms)	0.49	0.0039*	0.36	0.038*
P100 amplitude (uv)	-0.92	< 0.0001*	-0.95	< 0.0001*

Discussion

Visual dysfunctions linked to PD are demonstrable in the early stages of the illness, these dysfunctions are subtle

Table 4: Comparison between studied groups according to RNFL thickness mean values.

	Group 1	Group 2	Group 3	p- value
Average RNFL thickness (µm)				
Right eye	90.30 ± 0.73	87.1 ± 1.09	94.33 ± 0.55	< 0.0001*
Left eye	90.30 ± 0.48	85.35 ± 0.61	94.4 ± 0.44	< 0.0001*
Superior RNFL thickness (µm)				
Right eye	111.1 ± 0.73	106.9 ± 1.62	117.4 ± 1.43	< 0.0001*
Left eye	111.2 ± 0.91	106.4 ± 1.31	117.5 ± 0.84	< 0.0001*
Inferior RNFL thickness (µm)				
Right eye	106.7 ± 0.99	98.5 ± 1.62	110.4 ± 1.07	< 0.0001*
Left eye	107.5 ± 0.52	98.25 ± 1.42	110.4 ± 0.99	< 0.0001*
Nasal RNFL thickness (µm)				
Right eye	72.6 ± 1.26	72.83 ± 0.83	76.6 ± 1.95	< 0.0001*
Left eye	72.6 ± 0.96	72.92 ± 0.99	76.56 ± 1.13	< 0.0001*
Temporal RNFL thickness (µm)				
Right eye	68.2 ± 1.22	63.08 ± 1.56	73 ± 1.15	< 0.0001*
Left eye	68 ± 1.05	63.58 ± 1.78	73.2 ± 1.39	< 0.0001*

Table 5: Correlation between severity of the disease and OCT variables and both patients groups.

	Severity (H and Y scale)		Duration of the disease	
	R	***P***	***r***	***P***
Average RNFL thickness	-0.74	< 0.0001*	-0.78	< 0.0001*
Superior RNFL thickness	-0.67	< 0.0001*	-0.66	< 0.0001*
Inferior RNFL thickness	-0.81	< 0.0001*	-0.84	< 0.0001*
Nasal RNFL thickness	-0.35	0.049*	-0.79	< 0.0001*
Temporal RNFL thickness	-0.71	< 0.0001*	-0.74	< 0.0001*

Table 6: Correlation between VEP (P100 latency and amplitude) and retinal nerve fibers thickness evaluated by OCT in both patients groups.

	P100 latency (ms)		P100 amplitude (uv)	
	R	***P***	***R***	***P***
Average RNFL thickness	-0.92	< 0.00001*	0.87	< 0.00001*
Superior RNFL thickness	-0.88	< 0.00001*	0.81	< 0.00001*
Inferior RNFL thickness	-0.93	< 0.00001*	0.89	< 0.00001*
Nasal RNFL thickness	-0.535	0.0003*	0.50	0.0007*
Temporal RNFL thickness	-0.90	< 0.00001*	0.86	< 0.00001*

and could be easily detected through electrophysiological testing such as; the VEP and structural imaging by OCT which provide widely non-invasive techniques to evaluate the functional changes of the visual pathway, optic nerve and retinal changes in PD patients [8].

Aiming to study changes in the visual pathway and investigating the utility of these changes as disease progression biomarkers in PD patients, we recruited both drugs naïve newly diagnosed and medicated PD patients in different stages of the disease. Other healthy control subjects were recruited to compare our findings. Drug naïve PD patients were selected for two reasons first; to assess if visual pathway changes occur early in the disease course, second; to negate the possibility of medication effect on these changes, as the previous study by Bhaskar et al. [9] who reported improvement of VEP parameters after 3 months of L-dopa treatment.

VEP is a potential change detected in the visual cortex in response to retinal light stimulation and reflects the functional integrity of the visual pathway. The latency of the VEP is less likely to be affected by dopaminergic drugs and seems to be a more sensitive tool for evaluation of foveal electrical activity than VEP amplitude [10]. Abnormally prolonged latencies are caused by delayed conduction in visual pathways secondary to demyelination and/or plaque formation. The P100 latency of VEP is widely used in clinical practice to determine the abnormalities of the visual pathway due to the relatively minimal individual difference [11].

The present study result indicated that the N75, P100, N145 components of VEP had more prolonged latencies in PD patients than controls, also P100 amplitude was diminished in patients with PD than controls. The result of Pearson's correlation test in this study showed that the N75, P100, N145 latency was positively correlated with progression in duration and severity of the disease measured by Hoehn and Yahr scale. Also, the P100 amplitudes were negatively correlated with disease duration and severity.

These results of VEP are in agreement with the findings of Bodis-Wollner et al. [12] who reported that N75, P100, N145 components of VEP had more prolonged latency in PD patients than controls, also the P100 amplitude was decreased in patients with PD than controls and these changes were significantly correlated with disease progression and duration.

On the other side, the results of Liu et al. [13] study showed that the latencies of P100, N75, and N145 were more delayed in patients with PD than controls, but the amplitude of P100 was not significantly different between the PD patients and control subjects. Despite that, the P100 latency was positively correlated with the disease stage.

The loss of retinal dopaminergic neurons is considered as the main pathological process of visual function impairment in PD patients. Progressive dopaminergic retinal deficiency results in loss of retinal amacrine cells that provide input to retinal ganglion cells. Also, the higher visual cortex and a lateral geniculate nucleus that contain dopaminergic cells are susceptible to PD pathology [14].

Abnormal VEP parameters in PD patients reflect the diffuse nature of biochemical disturbance affecting both the central nervous system and the retina [13]. Thus, we used the OCT to analyze the RNFL in patients with PD.

OCT is a reliable fast, cost-effective and non-invasive method that provides a quantitative evaluation of the RNFL thickness around the optic nerve head and is considered as one

of the most useful clinical tools for diagnosing and monitoring the progression of neurodegenerative pathologies [15].

Nguyen-Legros [16] experimental study proposed that progressive retinal dopaminergic cell loss results in the impaired retina to cortex input, as retinal ganglion cells axons project via the optic nerve to diverse brain regions. The reduction of retinal ganglion cells related to dopamine deficiency and abnormal glutamate production leads to a corresponding decrease in retinal and RNFL thicknesses that can be detected in PD patients using OCT [17].

The current study results regarding SD-OCT findings showed a significant reduction in average RNFL thickness (superior RNFL, inferior RNFL, nasal RNFL, temporal RNFL thickness) in PD patients than healthy controls. Our results showed that these OCT findings were more affected as PD progress, which may highlight the importance of clinical utility of OCT in diagnosis and follow up of PD patients.

A meta-analysis reported a substantial decrease in average circumpapillary RNFL in PD patients compared to healthy subjects. Moreover, further analysis provided evidence that there were significant differences of RNFL thickness between the studied groups in superior, inferior, temporal, and nasal quadrants. However; one of the most important findings of that study was; the different types of OCT apparatus may result in different results. Despite that, subgroup analyses showed significant differences of RNFL thickness in average and temporal quadrant irrespective of the types of OCT apparatus. While the other three quadrants showed non-significant differences with certain kinds of OCT. One of the explanations of that finding maybe that temporal fibers are characteristically vulnerable to neurodegenerative pathologies [18].

In 2017, five years follow up study of peripapillary thicknesses assessed with SD-OCT in PD patients compared to control subjects was published by Satué et al. [19]. According to them; PD patients exhibited baseline RNFL thinning in the superior temporal and inferior temporal sectors, without significant reduction in macular thickness. After follow-up for 5 years, thinning was greater in the superior temporal sectors and in the macular area which was in a significant correlation with disease progression.

In another research by Garcia-Martin et al. [17] PD patients showed statistically significant reduced thickness in the RNFL, ganglion cell, plexiform layers, and increased thickness in the inner nuclear layer compared with healthy subjects.

Few studies assessed both visual functions and RNFL in PD patients. Altintas et al. [20] found a non-significant difference in the VEP P100 latencies between PD patients and control subjects. However, the RNFL thicknesses in all macular quadrants of PD patients, except fovea, were thinner than control subjects. These thinning was more prominent in the superior inner macula; temporal, nasal, and inferior quadrants of the outer macula. They also reported a nearly significant negative correlation between average macular volume and P100 latency in PD patients, while RNFL was not correlated to P100 and PD duration, which could be explained by their small sample of patients and the statistical methods they used and different methodology as they applied UPDRS rather than Horhn and Yahr staging system.

Hasanov et al. [21] evaluated and followed-up optic nerve functions and ocular morphological changes in early-stage PD patients, and reported that P100 wave latency was significantly prolonged, and its amplitude was decreased in the patients' group; however, no significant deterioration was observed during the follow-up. While the mean macular thickness and total macular volume values were not initially different among the groups, the patient group developed a significant thinning during the follow-up.

The current study showed that there was a significant correlation of visual dysfunction evaluated by VEP and morphological changes of the retina and optic nerve measured by OCT. Furthermore we report a significant association between delayed P100 latencies and decreased in the RNFL thickness.

Finally, there was a significant association between decreased P100 Amplitudes and the average RNFL thickness. These results confirm and give extra supportive evidence to the current knowledge regarding the high vulnerability of the visual pathway in PD patients.

Our results indicated that the changes in both VEP and RNFL thickness are correlated with disease duration and severity and not affected by medication, and they represent good candidate biomarkers in the evaluation and follow up of Parkinson's disease progression.

Conclusion

Our results indicate PD patients either drug naïve or medicated show functional and morphological changes in the visual pathway, these changes could be easily detected by non-invasive tools such as VEP and OCT. Therefore, these changes represent new biomarkers for follow up of PD patients as the current study results found a significant correlation between VEP/OCT changes and PD progression.

Limitation

We don't know if our conclusion would differs if we recruited PD patient suffering other co-morbidities or not. There is a concern regarding racial effect on RNFL thickness (our patient were only Caucasian).

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