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The effect of levodopa and dopamine agonists on optic nerve head in Parkinson disease

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PURPOSE. *To evaluate the effects of levodopa and dopamine agonists on retinal nerve fiber layer using scanning laser ophthalmoscope.*
METHODS. *Forty-four patients with the diagnosis of Parkinson disease and receiving levodopa or dopamine agonist monotherapy were included in this prospective study. The control group consisted of 21 normal cases. The optic nerve head images were taken with Heidelberg Retina Tomograph; rim area, rim volume, mean retinal nerve fiber layer thickness, and the results of Moorfields regression analysis were calculated. The measurement results were evaluated with Kruskal Wallis test and Mann-Whitney U-test.*
RESULTS. *There was no significant difference in mean age among groups (p=0.093). Retinal nerve fiber layer was measured to be significantly decreased in cases with Parkinson disease (p=0.004) while rim area and rim volume did not show a significant change (p=0.224, p=0.804 respectively). Rim area, rim volume, and retinal nerve fiber layer were significantly greater in the group treated with levodopa while it was the thinnest in the group receiving dopamine agonists.*
CONCLUSIONS. *Levodopa can have a protective affect to retinal nerve fiber layer in Parkinson disease compared to dopamine agonists. (Eur J Ophthalmol 2007; 17: 812-6)*

KEY WORDS. *Dopamine agonists, Levodopa, Parkinson disease, Retinal nerve fiber layer*

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INTRODUCTION

Parkinson disease (PD) is the second most common neurodegenerative disease after Alzheimer disease over the age of 65 years. PD is associated with degeneration of dopaminergic neurons in substantia nigra. Dopamine has been shown to have a neuromodulator and neurotransmitter role in the retina (1). Dopamine is mostly found in amacrine cells and interplexiform cells. It was first shown by Harnois and Di Paolo that retinal dopamine concentration decreased in PD (2). Visual abnormalities have been shown in early stages of PD due to retinal dopaminergic deficiency (3). As PD is a progressive disease, the goal of therapy is to slow progression and restore neuronal function (4). Levodopa, which is a dopamine precursor, is the gold standard drug being used in PD today. Dopamine receptor agonists are being preferred in the early stages of PD for dopaminergic replacement therapy because levodopa can have motor complications when used for a long period in patients with PD (5). It is suggested that dopamine agonists (DAs) also may have neuroprotective effects (3).

It is known that retinal dopamine deficiency produces abnormalities in retinal ganglion cell function (6). Any damage or loss in retinal ganglion cells will lead to retinal nerve fiber layer (RNFL) changes. Heidelberg Retina Tomograph (HRT) is a confocal laser scanning system that measures and analyzes three-dimensionally the optic nerve head and RNFL. Heidelberg Retina Tomograph acquires a series of optical section images at different locations of the focal plane. Heidelberg Retina Tomograph provides objective and quantitative information about optic nerve head and the thickness of peripapillary RNFL (7). In this study, we evaluated the effect of levodopa and DAs

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on retinal nerve fiber layer using HRT II and compared this with normal subjects.

METHODS

The study was planned as a prospective study. Forty-four patients with PD and receiving levodopa or DA (pramipexole) monotherapy for at least 6 months (16 patients receiving levodopa and 28 patients receiving pramipexole) were included in the study. The control group consisted of 21 normal cases who did not have any ocular or systemic disease. The right eye of each patient was included in the study. Cases with a visual acuity lower than 20/30, a history of ocular trauma, uveitis, intraocular surgery, media haze like cataract, glaucoma and any systemic disease that could affect the evaluation of optic nerve head, or any medication use known to affect visual function were excluded from the study.

Diagnosis of PD was done according to UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (8). The optic nerve head of all eyes was imaged using a scanning laser ophthalmoscope (HRT II, Heidelberg Engineering, Germany). All images were acquired by the same observer, with the patient fixating at the internal fixating target of the instrument. The imaging head and eye distance was approximately 10 mm. After the images were obtained, the disc margin contour was marked. Rim area (mm^2), rim volume (ccm), and mean RNFL thickness (mm) and the results of Moorfields regression analysis were calculated. Temporal, superotemporal, inferotemporal, nasal, superonasal, and inferonasal values were calculated for these three parameters. The cases with PD were also compared with control group without subdividing into treatment groups.

Statistical analysis was performed using SPSS 10.0 statistical program. The sex distribution among groups was evaluated with chi-square test. The measurement results were evaluated with Kruskal Wallis test. The comparison between groups was done using Mann-Whitney *U* test. p Values lower than 0.05 were determined to be significant.

RESULTS

Mean age was 69.14±2.54 years in the control group, 70.75±4.79 years in the group receiving levodopa, and 71.86±4.79 years in the group receiving DAs (p=0.093).

When the cases with PD were compared with control group without classifying into subgroups according to the treatment modality, rim area and rim volume did not show a significant change among groups (p=0.22, p=0.80, respectively). There was not any significant difference in the sectorial analysis for these parameters. The difference of RNFL thickness between cases with PD and control group was statistically significant (p=0.004). RNFL thickness was found to be decreased in cases with PD. Moorfields regression analysis revealed significant difference in the nasal, superonasal, inferonasal, and inferotemporal sectors (p=0.018, p=0.002, p=0.004, p=0.034, respectively). The difference in RNFL thickness was not significant for temporal and superotemporal sectors (p=0.23, p=0.058, respectively).

The difference between the mean duration of treatment was not significant among treatment groups (p=0.26). The mean duration of treatment was 15.07±4.9 months in the group treated with levodopa and 15.81±4.5 months in the group treated with DAs. Rim area, rim volume, and RNFL thickness measured in treatment and control groups are given in Table I.

Rim area was significantly greater in the group treated with levodopa while it was the thinnest in the group receiving DAs (Tab. I). There was only a significant change in superonasal and inferonasal sectors among control group and levodopa group (Tab. II). When compared with control group and levodopa group, rim area was significantly thinner in the DA group (Tab. II).

Rim volume was also significantly greater in the group receiving levodopa while it was the thinnest in the group receiving DAs (Tab. I). The comparison between groups was similar with the rim area measurement results (Tab. III).

RNFL was also significantly greater in the group receiving levodopa and thinner in the group receiving DAs (Tab. I). The difference was significant in all measured sectors except the temporal sector. The comparison between groups was the same with rim area and rim volume measurements (Tab. IV).

DISCUSSION

Neurodegenerative diseases can affect the visual system in several ways. The cortical degeneration characteristics in Alzheimer disease are also present in the visual cortical areas which mostly lead to higher-order visual disabilities whereas in PD dopamine deficiency leads to higher-order

TABLE I - MOORFIELDS REGRESSION ANALYSIS

	Control	Levodopa	DA	p*
Rim area (mm2)	1.53 ± 0.38	1.87 ± 0.48	1.52 ± 0.29	0.018
Rim area temporal	0.27 ± 0.11	0.36 ± 0.15	0.30 ± 0.08	0.11
Rim area superotemporal	0.19 ± 0.05	0.23 ± 0.08	0.20 ± 0.05	0.43
Rim area inferotemporal	0.20 ± 0.06	025 ± 0.08	0.19 ± 0.05	0.034
Rim area nasal	0.44 ± 0.11	0.50 ± 0.09	0.43 ± 0.06	0.097
Rim area superonasal	0.22 ± 0.05	0.26 ± 0.07	0.20 ± 0.04	0.006
Rim area inferonasal	0.22 ± 0.05	0.25 ± 0.08	0.20 ± 0.08	0.10
Rim volume (ccm)	0.44 ± 0.14	0.56 ± 0.23	0.37 ± 0.13	0.026
Rim volume temporal	0.03 ± 0.02	0.05 ± 0.03	0.03 ± 0.01	0.15
Rim volume superotemporal	0.05 ± 0.02	0.08 ± 0.07	0.04 ± 0.02	0.15
Rim volume inferotemporal	0.06 ± 0.04	0.06 ± 0.04	0.04 ± 0.02	0.41
Rim volume nasal	0.14 ± 0.04	0.18 ± 0.06	0.11 ± 0.04	0.026
Rim volume superonasal	0.09 ± 0.11	0.13 ± 0.14	0.12 ± 0.22	0.047
Rim volume inferonasal	0.07 ± 0.02	0.09 ± 0.04	0.10 ± 0.15	0.36
RNFL (mm)	0.28 ± 0.05	0.28 ± 0.10	0.20 ± 0.05	<0.001
RNFL temporal	0.09 ± 0.02	0.09 ± 0.01	0.08 ± 0.02	0.067
RNFL superotemporal	0.32 ± 0.08	0.27 ± 0.09	0.26 ± 0.07	0.036
RNFL inferotemporal	0.32 ± 0.08	0.36 ± 0.36	0.21 ± 0.11	0.005
RNFL nasal	0.32 ± 0.07	0.31 ± 014	0.21 ± 0.10	0.001
RNFL superonasal	0.38 ± 0.08	031 ± 0.08	0.30 ± 0.09	0.004
RNFL inferonasal	0.40 ± 0.07	0.31 ± 0.13	0.27 ± 0.10	<0.001

Bold values are significant
*Kruskal Wallis test.
DA = Dopamine agonist; RNFL = Retinal nerve fiber layer

TABLE II - RIM AREA MEASUREMENTS AMONG GROUPS

	Control-levodopa	Control-DA	Levodopa-DA
Rim area	0.75	<0.001	0.010
Temporal	0.61	0.089	0.046
Superotemporal	0.24	0.014	0.29
Inferotemporal	0.24	0.001	0.15
Nasal	0.23	0.002	0.009
Superonasal	0.005	0.010	0.50
Inferonasal	0.014	<0.001	0.25

Bold values are significant.
Statistical analysis was done by Mann-Whitney U-test.
DA = Dopamine agonist

TABLE III - RIM VOLUME MEASUREMENTS AMONG GROUPS

	Control-levodopa	Control-DA	Levodopa-DA
Rim volume	0.75	<0.001	0.010
Temporal	0.61	0.089	0.046
Superotemporal	0.24	0.014	0.29
Inferotemporal	0.24	0.001	0.15
Nasal	0.23	0.002	0.009
Superonasal	0.005	0.010	0.50
Inferonasal	0.014	<0.001	0.25

Bold values are significant.
Statistical analysis was done by Mann-Whitney U-test.
DA = Dopamine agonist

visual abnormalities and retinal ganglion cell dysfunction (6, 9). In retina, dopamine is found mainly in amacrine and interplexiform cells (1). Retinal dopamine concentration decreases significantly and retinal dopaminergic mechanisms are significantly impaired in cases with PD (2, 10). Several visual dysfunctions have been reported in PD (10-14). Diederich et al (12) showed that contrast sensitivity was impaired in PD. Jaffe et al (15) compared the Ganzfield electroretinogram (ERG) results from the eye ipsilateral to the more affected side with those from the contralateral side in cases with PD and reported that there was an increase in the latency of the short wavelength

TABLE IV - RETINAL NERVE FIBER LAYER (RNFL) MEASUREMENTS AMONG GROUPS

	Control-levodopa	Control-DA	Levodopa-DA
RNFL	0.75	<0.001	0.010
Temporal	0.61	0.089	0.046
Superotemporal	0.24	0.014	0.29
Inferotemporal	0.24	0.001	0.15
Nasal	0.23	0.002	0.009
Superonasal	0.005	0.010	0.50
Inferonasal	0.014	<0.001	0.25

Bold values are significant.
Statistical analysis was done by Mann-Whitney U-test.
DA = Dopamine agonist

sensitive cone response recorded from the retina ipsilateral to their more symptomatic side. In contrast, Palmowski-Wolfe et al (16) reported that contrast sensitivity and multifocal ERG did not show a remarkable change in patients with PD. Inzelberg et al (17) evaluated the peripapillary RNFL using optical coherence tomography and showed that the thickness in the inferior quadrant of patients with PD was significantly thinner compared to control subjects. In our study, rim area and rim volume did not show a significant change in cases with PD while the RNFL thickness was found to be decreased especially in the nasal and inferior sectors of the optic nerve head.

In this study, we found that levodopa had a protective effect on RNFL in PD. Rim area, rim volume, and RNFL thickness were measured to be increased in superonasal and inferonasal sectors in the group using levodopa compared to control group. When the treatment groups were compared, temporal and nasal sectors were found to be decreased in the group using DA. The decrease in RNFL thickness in the group using DA was significant in all sectors except temporal sector when compared with control group. It is our drawback not to collect data on untreated PD subjects but the comparison of treatment groups with normal age-matched subjects provides reliable data.

Johnson et al (18) reported that levodopa was beneficial in the treatment of nonarteritic anterior ischemic optic neuropathy and visual acuity showed significant improvement compared to control group. Murer et al (19) showed in an experimental model of PD that 6-month oral levodopa treatment was not toxic for the remaining dopamine neurons and promoted the recovery of striatal innervation. Buttner et al (20) showed that color vision improved after the oral administration of levodopa. Jaffe et al (15) reported an improvement in the ERG responses following levodopa infusion in cases with PD. We observed a neuroprotective effect of levodopa on RNFL in cases with PD using levodopa monotherapy for at least 6 months.

In PD, there is a trend for agonist monotherapy rather than levodopa because of the reduced incidence of motor complications (21). DAs produce their symptomatic effects by binding directly with the postsynaptic dopamine receptors (22). DAs are believed to have a neuroprotective effect (22, 23). We could not observe a neuroprotective effect of DAs on RNFL in patients with PD.

Various types of dopamine receptors, especially D_1 and D_2 subtypes, are located on retinal neurons (9). Newman-Tancredi et al (24) evaluated the efficacy of various DAs where drug efficacy was expressed as a percentage of the effect observed with a maximal concentration of dopamine. No ligand displayed full efficacy relative to dopamine (100%) at all D_2 sites. Pramipexole was reported to be as effective as dopamine for only D_{2S} receptors while its efficacy for D_{2L}, D_3, and D_4 receptors was lower (70% 70%, 40%, respectively). As levodopa is a precursor of dopamine, its efficacy to all subtypes of dopamine receptors will be 100%. This may be why we found levodopa to have more protective effect on RNFL compared to DAs. To our knowledge, this is the first study to show that levodopa has a protective effect on RNFL in PD compared to DAs.

Proprietary interest: None.

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