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Original Article

Ophthalmology Section

Macular Thickness Evaluation in Parkinson's Disease using Spectral Domain Optical Coherence Tomography: A Case-control Study

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ABSTRACT

Introduction: Parkinson's Disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. Its incidence is increasing worldwide, along with population aging and a longer life span. Since the retina is part of the Central Nervous System, the dopaminergic cells are present in the retina too.

Aim: To evaluate central macular thickness, average macular thickness, and macular volume changes in Parkinson's cases and compare them with age and gender matched healthy control group using Spectral Domain Optical Coherence Tomography (SD-OCT).

Materials and Methods: This was a case-control study, conducted from January 2019 to October 2020 in the Department of Ophthalmology and the Department of Neurology Outpatient Department (OPD) of Government Regional Eye Hospital, Andhra Medical College, Visakhapatnam, Andhra Pradesh, India. Total 50 diagnosed cases of PD using the United Kingdom Parkinson's Disease Society Brain Bank criteria were included in the study. Fifty age and the gender matched healthy group were included as controls. Both groups underwent retinal imaging with SD-OCT using Macular scans with 6 mm in diameter, centered at the foveola measuring macular thickness and macular volume averages for each of the nine map areas and data was incorporated into a logistic regression model to predict changes. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 22.0 (released 2013 Armonk, NY: IBM Corp.).

Results: There were 24 male and 26 female in both the groups, with maximum in the age group of 51-60 years. There was no significant difference between the various groups in terms of the age and gender. There was a significant difference between the two groups in terms of central macular thickness (W=549.0, p-value <0.001), with the median central macular thickness (µm) being highest in the control group. There was a significant difference between the two groups in terms of macular volume (cumm) (t=-5.193, p-value <0.001), with the mean macular volume (cumm) being highest in the control group. There was no significant difference between the groups in terms of average macular thickness (µm) (W=1534.000, p-value=0.050). However, for every one unit increase in duration of disease (years), the average macular thickness (µm) decreases by 2.70 units (rho=-0.64, p-value <0.001).

Conclusion: The macular thickness decreases with increasing disease duration in patients with PD patients compared to age and gender matched.

Keywords: Dopaminergic cells, Neurodegenerative disorder, Retinopathy

INTRODUCTION

Parkinson's Disease (PD) is an advanced neurodegenerative disorder with selective dopaminergic neuronal loss in the substantia nigra [1]. Studies done previously have demonstrated dopamine dysfunction in the retina as well as in basal ganglia [2,3].

Non invasive evaluation of the human retina can be done using Spectral Domain Optical Coherence Tomography (SD-OCT); thus, this technique has been proposed to monitor PD within the retina [4]. Previous studies have used SD-OCT in PD patients, but with contradictory results; for instance, the retinal thickness has been recommended by some to be reduced in PD patients versus controls [4-6]. One of the main advantages of SD-OCT is its ability to resolve individual cell layers in the retina, provide a measure of the integrity of the retinal ganglion cell axons as they exit the retina, and give information on macular morphology.

Previous studies using OCT have demonstrated morphological changes in retinal structure in multiple sclerosis, Alzheimer's disease, and PD [7,8]. Retinal nerve fiber thinning has been found in PD [9], and macular thickness has also been reduced though in a relatively small number of patients [10,11]. One possible explanation for these findings is that dopaminergic deficiency deprives the retina of key trophic factors, which is vital to maintain structural integrity [12].

To date, the functional implications of these reported morphological changes are unclear. Therefore, authors compared retinal structure in a PD and healthy age and gender matched control cohort for indication of macular thinning and evaluated the utility of OCT for disease progression in PD.

MATERIALS AND METHODS

This case-control study was conducted from January 2019 to October 2020 in the Department of Ophthalmology and the Department of Neurology Outpatient Department of Government Regional Eye Hospital, Andhra Medical College, Visakhapatnam, Andhra Pradesh, India. Ethical society clearance number (EC/NEW/INST/2019/397) was obtained before conducting the study.

Sample size calculation: The sample size was calculated using the following formula:

$n=(Z_{1-\alpha/2}+Z_{1-\beta})^2 * \sigma^2/d^2$ [13]

Where, $Z_{1-\alpha/2}$ is the critical value of the normal distribution at $\alpha/2$,

$Z_{1-\beta}$ is the critical value of the Normal distribution at β,

σ^2 is the population variance, and d is the difference you would like to detect.

Based on the above formula, the sample size is 42.

Considering 20% of dropouts, final sample size was considered to be 50. Total 50 PD and 50 age and gender matched healthy control group were included for the study.

Inclusion criteria

For case: The United Kingdom Brain Bank criteria were used to diagnose PD [14] in the age group of 40-80 years, and those who gave written informed consent were included in the study.

For control: Inclusion criteria of the control group are the age matched and gender matched group with no ocular or systemic pathology and giving consent to undergo examination were included in the study.

Exclusion criteria

All cases with intraocular pressure >21 mmHg, known case of glaucoma, history of surgery for glaucoma, or history of use of antiglaucoma medication, history of macular pathology or retinopathy, history of demyelinating or other neurodegenerative diseases, and media opacity precluding Optical Coherence Tomography (OCT) imaging were excluded from the study.

All controls with history of chronic ocular medication use, intraocular surgery, previous retinal pathology, uncontrolled diabetics, and hypertensive were excluded from the study.

Procedure

Each PD patient underwent a neurological examination on the same day. The disease severity was evaluated using the Unified Parkinsons Disease Rating Scale [15], which scores cognitive disturbances, activities of daily living, and motor features of PD like tremor, rigidity, bradykinesia, and postural disorders.

An ophthalmologic examination, including anterior segment biomicroscopy, visual acuity, applanation tonometry, and visual fields, were done to rule out glaucoma. Fundus examination was done to rule out posterior segment pathologies after dilating the pupil with 10% phenylephrine and 1% tropicamide, with the help of an indirect ophthalmoscope or 78 D lens.

The central macular thickness, average macular thickness, and macular volume were measured by commercially available Cirrus Spectral Domain-OCT 5000 acquiring macular scans using the macular cube 512×128 scan protocol [16]. Macular scans with 6 mm in diameter, centered at the foveola measuring macular thickness and macular volume averages for each of the nine map sectors as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) [17]. The inner and outer rings were segmented into four quadrants, with radii of 1.5 mm and 3 mm, respectively.

The patient was seated with comfort, with the chin on the chin rest and forehead against a curved strap. The manufacturer recommends a pupil diameter of 3.2 mm. The room lights were dimmed, and in most cases, the scanning can be done without the need for dilatation. In the presence of media opacities, pupillary dilatation is a must; otherwise, the signal strength will not be accurate. However, a pupillary size of 3 mm is adequate for most purposes in the presence of clear optical media. Only good-quality scans, defined as scans with signal strength ≥6, were used for the analysis.

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS) version 22.0 (released 2013 Armonk, NY: IBM Corp.) was used to perform statistical analyses. Descriptive analysis was done using frequency and proportions for categorical variables. The mean and Standard Deviation (SD) were used for continuous variables. The Chi-square test was used to compare different study variables on categorical distribution between the two study groups. Mann-Whitney test was used to compare the mean scores of different study variables with continuous distribution between the two study groups. Paired t-test was used to compare mean scores of different scales of important study variables within each study group. The confidence interval was set at 95%. The level of significance in the study was set at a p-value <0.05.

RESULTS

There were 24 male and 26 female in both the groups, with maximum in the age group of 51-60 years. There was no significant difference between the groups in terms of the distribution of the age group [Table/Fig-1].

Age group (years)	Groups			Fisher's-exact test	
	Case	Control	Total	χ^2	p-value
41-50	6 (12%)	7 (14%)	13 (13%)	0.410	1.000
51-60	23 (46%)	23 (46%)	46 (46%)		
61-70	19 (38%)	19 (38%)	38 (38%)		
71-80	2 (4%)	1 (2%)	3 (3%)		
Total	50 (100%)	50 (100%)	100 (100%)		

[Table/Fig-1]: Association between group and age group (N=100).

There was no significant difference between the groups in terms of the distribution of gender [Table/Fig-2]. The mean duration of disease was 4.63±2.9.

Gender	Groups			Chi-square test	
	Case	Control	Total	χ^2	p-value
Male	24 (48%)	24 (48%)	48 (48%)	0.000	1.000
Female	26 (52%)	26 (52%)	52 (52%)		
Total	50 (100%)	50 (100%)	100 (100%)		

[Table/Fig-2]: Association between group and gender (N=100).

The mean (SD) of central macular thickness (µm) in the case group was 215.58 (15.13). The mean (SD) of central macular thickness (µm) in the control group was 228.70 (10.65). There was a significant difference between the two groups in terms of central macular thickness (µm) (W=549.000, p-value <0.001), with the median central macular thickness (µm) being highest in the control group [Table/Fig-3].

Central macular thickness (µm)	Groups		Wilcoxon Mann-Whitney U-test	
	Case	Control	W	p-value
Mean (SD)	215.58 (15.13)	228.70 (10.65)	549.000	<0.001
Median (IQR)	216 (211.25-223.5)	228 (221.25-232)		
Range	168-252	208 - 254		

[Table/Fig-3]: Comparison of the 2 subgroups of the variable group in terms of central macular thickness (µm) (N=100).
p-value <0.05 considered significant

The mean (SD) of average macular thickness (µm) in the case group was 237.64 (9.91). The mean (SD) of average macular thickness (µm) in the control group was 240.34 (12.96). There was no significant difference between the groups in terms of average macular thickness (µm) (W=1534.000, p-value=0.050) [Table/Fig-4].

Average macular thickness (µm)	Group		Wilcoxon-Mann-Whitney U Test	
	Case	Control	W	p-value
Mean (SD)	237.64 (9.91)	240.34 (12.96)	1534.000	0.050
Median (IQR)	238 (230-245)	243.5 (232.75-248.75)		
Range	204-258	218-258		

[Table/Fig-4]: Comparison of the 2 subgroups of the variable group in terms of average macular thickness (µm) (N=100).

The mean (SD) of macular volume (cumm) in the case group was 9.79 (1.32). The mean standard deviation of macular volume (cumm) in the control group was 10.87 (0.66). There was a significant difference between the two groups in terms of macular volume (cumm) (t =-5.193, p-value <0.001), with the mean macular volume (cumm) being highest in the control group [Table/Fig-5].

Non parametric tests (Spearman correlation) were used to explore the correlation between the two variables, as atleast one of the variables was not normally distributed.

Macular volume (cumm)	Group		t-test	
	Case	Control	t	p-value
Mean (SD)	9.79 (1.32)	10.87 (0.66)	-5.193	<0.001
Median (IQR)	9.8 (8.9-10.8)	10.8 (10.4-11.4)		
Range	6.8 - 12.4	9.4 - 12.5		

[Table/Fig-5]: Comparison of the 2 subgroups of the variable group in terms of macular volume (cumm) (N=100).
p-value <0.05 considered significant

There was a moderate negative correlation between central macular thickness (µm) and duration of disease (years), and this correlation was statistically significant (rho=-0.52, p-value <0.001), as shown in [Table/Fig-6]. For every one unit increase in duration of disease (years), the central macular thickness (µm) decreases by 2.69 units.

Correlation	Spearman correlation coefficient	p-value
Central macular thickness (µm) vs. duration of disease (years)	-0.520	<0.001

[Table/Fig-6]: Correlation between central macular thickness (µm) and duration of disease (years) (n=50).
p-value <0.05 considered significant

There was a strong negative correlation between average macular thickness (µm) and duration of disease (years), and this correlation was statistically significant (rho=-0.64, p-value <0.001), as shown in [Table/Fig-7]. For every 1 unit increase in duration of disease (years), the average macular thickness (µm) decreases by 2.70 units.

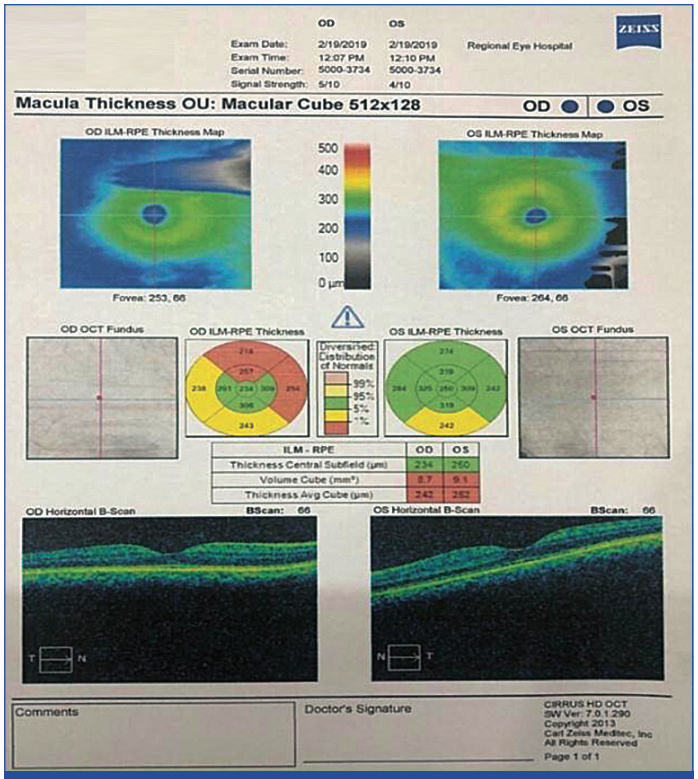
Correlation	Spearman correlation coefficient	p-value
Average macular thickness (µm) vs. Duration of disease (Years)	-0.640	<0.001

[Table/Fig-7]: Correlation between average macular thickness (µm) and duration of disease (years) (n=50).
p-value <0.05 considered significant

There was a moderate negative correlation between macular volume (cumm) and duration of disease (years), and this correlation was statistically significant (rho=-0.49, p-value <0.001), as shown in [Table/Fig-8]. For every 1 unit increase in duration of disease (years), the macular volume (cumm) decreases by 0.25 units. OCT Images for reference [Table/Fig-9].

Correlation	Spearman correlation coefficient	p-value
Macular volume (cumm) vs Duration of disease (years)	-0.490	<0.001

[Table/Fig-8]: Correlation between macular volume (cumm) and duration of disease (years) (n=50).
p-value <0.05 considered significant



[Table/Fig-9]: Image of optical coherence tomography scan of macular thickness showing severely reduced thickness in the superior and nasal quadrant in the right eye and moderate reduction in the inferior quadrant in both the eyes.

DISCUSSION

The neuronal loss has not only been seen in substantia nigra but in other varied populations of dopaminergic neurons. Retinal ganglia cells and the projections of dopaminergic pathways to the cortex are dopaminergic areas and PD is supposed to be caused by the loss of dopaminergic neurons in the retina [17,18,19]. Higher visual areas, lateral geniculate nucleus, and visual cortex containing dopaminergic cells may also be susceptible to PD [20].

The macula is defined anatomically as the region in the retina where the ganglion cell layer is more than one cell thick. [21]. Hence, it was expected that macular volume and thickness would be reduced in PD patients. In this study, the mean standard deviation of age (years) in the PD group and control group was 58.28. Maximum participants are in the age group of 51-60 years (46%).

In the present study, the mean standard deviation of central macular thickness (µm) in the PD group was 215.58 and in the control group was 228.70, respectively. There was a significant difference between the two groups in terms of central macular thickness (µm) (W=549.000, p-value <0.001), with the median central macular thickness (µm) being highest in the control group. For every 1 unit increase in duration of disease (years), the central macular thickness (µm) decreases by 2.69 units. Similarly, in the Aker GD et al., study there was a significant difference in macular thickness in three out of nine subfields between PD subjects with outer superior subfield 2.8% thinner than punished normal value [4].

Altintas O et al., stated the first macular study in PD patients, in that there was a decreased superior segment thickness of the inner retinal layer and the temporal, nasal, and inferior segment of the Outer Retinal Layer (ORL) [9]. In this study, the mean standard deviation of average macular thickness (µm) in the PD group was 237.64 and in the control group was 240.34, respectively. There was no significant difference between the groups in terms of average macular thickness (µm) (W= 1534.000, p-value=0.050). For every 1 unit increase in duration of disease (years), the average macular thickness (µm) decreases by 2.70 units. Similarly, Hu Z et al., concluded that the IPL contributes less than 12% to the average thickness of the macular area. However, at the very center of the foveal pit, there is no contribution to the macular volume (or thickness) by the INL, Inner Plexiform Layer (IPL), and Ganglion cell layer [22]. Hence, the difference between PD and healthy control becomes evident only in an annular zone between 0.5 and 2 mm from the foveola.

In the present study, the mean standard deviation of macular volume (cu.mm) in the PD group was 9.79 and in the control group was 10.87, respectively. There was a significant difference between the two groups in terms of macular volume (cu.mm) (t=-5.193, p-value<0.001), with the mean macular volume (cu.mm) being highest in the control group. For every 1 unit increase in duration of disease (years), the macular volume (cu.mm) decreases by 0.25 units. Similar findings were reported by Altintas O et al., in which there was total macular volume reduction in 17 PD compared to 11 healthy control (6.82±0.32 mm^3 vs. 7.09±0.23 mm^3) [9].

The average central macular thickness and macular volume in the PD group were less than the control subjects. There was no difference observed in average macular thickness in the PD group and control group. However, with the increasing duration of the

disease, the average macular thickness decreased. Large-scale studies are compulsory to assess the correlation between structural, clinical, and functional findings in diverse clinical stages of PD as the dopamine level decreases in the visual pathways.

Limitation(s)

Patients in very early or pre-symptomatic stages of the disease were not taken into consideration.

CONCLUSION(S)

The study results suggest a significant reduction in central macular thickness, average macular thickness, and macular volume with increasing duration of disease in patients with PD patients compared to age, and gender matched healthy control group evaluated in-vivo by SD-OCT. In the era of non invasive methods of diagnosis, SD-OCT is a promising device for clinical settings.

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